STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

# Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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All authors read and commented on draft versions of the ERG report.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AEs | adverse events |
| CDF | Cancer Drugs Fund |
| CI | confidence interval |
| CS | company submission |
| CSR | clinical study report |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| EMBRACE | Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389 |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ER | oestrogen receptor |
| ERG | Evidence Review Group |
| FAD | final appraisal determination |
| HER2 | human epidermal growth factor receptor 2 |
| HRG | Healthcare Resource Group |
| HRQoL | health-related quality of life |
| ITT | intention-to-treat |
| IV | intravenous |
| K-M | Kaplan-Meier |
| LABC/MBC | locally advanced or metastatic breast cancer |
| NICE | National Institute for Health and Care Excellence |
| OS | overall survival |
| PAS | patient access scheme |
| PFS | progression-free survival |
| PH | proportional hazard(s) |
| PPS | post-progression survival |
| PS | performance status |
| RCT | randomised controlled trial |
| SAE | serious adverse event |
| STA | single technology appraisal |
| TPC | Treatment of Physician’s Choice |

# 1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process.

Clinical and economic evidence have been submitted to NICE by Eisai in support of the use of eribulin (Halaven®). Eribulin was appraised previously by NICE in 2012 (TA250). At that time eribulin was licensed for the treatment of adult patients with locally advanced or metastatic breast cancer (LABC/MBC) who had progressed after at least **two** chemotherapy regimens for advanced disease. Prior chemotherapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for these treatments. In 2014 the European Medicines Agency licence for treatment with eribulin was broadened to include less heavily treated patients. The new licence is for the treatment of adult patients with LABC/MBC who have progressed after at least **one** chemotherapeutic regimen for advanced disease. Again, prior chemotherapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for these treatments.

In July 2016 the company submitted evidence relating to two different subgroups of the licensed population, one relating to the licence that was valid in 2012 and the other to the 2014 licence. Following discussions between the company, NICE and the ERG, the scope of this STA was amended so that its only focus is a review of TA250. The remainder of this report is therefore only concerned with the evidence submitted by the company for a review of TA250.

## *1.1 Critique of the decision problem in the company's submission*

Clinical effectiveness evidence is derived primarily from the EMBRACE trial and is considered by the company for two populations:

- All patients receiving ≥3 chemotherapy regimens for LABC/MBC: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. This is the EMBRACE trial intention-to-treat (ITT) population.
- Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated). Prior treatment also includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. This is a subgroup (73%) of the EMBRACE trial and is referred to by the company (and within this ERG report) as Subgroup 2.

The populations are the same as those that were the final focus of the Appraisal Committee's TA250 final appraisal determination (FAD) document. However, the comparator for Subgroup 2 patients is different. For both populations in the current STA, the comparator to eribulin is Treatment of Physician's Choice (TPC), whereas in TA250, the comparators were TPC for all patients receiving ≥3 chemotherapy regimens for LABC/MBC and vinorelbine for Subgroup 2 patients. Although the ERG considers that vinorelbine is an appropriate comparator for patients previously treated with capecitabine, the use of TPC is pragmatic and more likely to reflect patient experience in England. The TPC administered during the EMBRACE trial included (but was not limited to) chemotherapy (93.7%) and hormonal therapy (3.5%). The comparators listed in the final scope issued by NICE were vinorelbine, capecitabine and gemcitabine. All three comparators were agents available in the TPC arm of the EMBRACE trial (59.4% of all TPC agents).

Cost effectiveness evidence is only presented for Subgroup 2 patients. As specified in the final scope issued by NICE, the cost effectiveness of eribulin was expressed in terms of the incremental cost per quality adjusted life year gained (QALY) gained. In the base case, outcomes were assessed over a 5-year time horizon, with scenarios considering 10- and 20-year horizons. Costs were considered from an NHS perspective. A simple patient access scheme (PAS), offering a straight discount to the list price, of eribulin was formally agreed with the Department of Health on 14 January 2016. This PAS price is used in the company's cost effectiveness analysis.

## *1.2 Summary of clinical effectiveness evidence submitted by the company*

Clinical effectiveness evidence is derived primarily from the EMBRACE trial, identified via the company's systematic review. This trial was a multi-centre, phase III, open-label, randomised parallel two-arm trial. The primary objective of the EMBRACE trial was to evaluate overall survival (OS) of patients treated with eribulin versus TPC in patients with LABC/MBC who had received two to five prior chemotherapy regimens. All patients were receiving ≥3 chemotherapy regimens for LABC/MBC.

A total of 762 patients were randomised in a 2:1 ratio to receive either eribulin (n=508) or TPC (n=254). Randomisation was stratified according to geographical region, human epidermal growth factor receptor 2 (HER2) status, and prior treatment with capecitabine. The selection of TPC agents took place prior to randomisation.

The median age of patients enrolled in the EMBRACE trial was 55 years. The majority were Caucasian (>90%) and post-menopausal (~75%). Most patients had oestrogen receptor (ER)-positive (~70%) and/or HER2-negative (~80%) disease and an Eastern Cooperative

Oncology Group (ECOG) performance status (PS) of 0 (~42%) or 1 (~48%). The most common sites for metastases were bone (>60%) and liver (>60%). Median time since diagnosis was just over 5 years. Patient characteristics appear to be well balanced across treatment groups. Nearly three-quarters (73%) of patients in the EMBRACE trial had previously received treatment with capecitabine; these are the patients that constitute the Subgroup 2 population.

At the time of the most recent data-cut of the EMBRACE trial (17 June 2013), all patients had discontinued study treatment and 95% of all patients had died. For the ITT population, median OS was 2.7 months longer for patients in the eribulin arm (13.24 months) than for patients in the TPC arm (10.55 months); whilst median progression-free survival (PFS) was 1.4 months longer for patients in the eribulin arm (3.61 months) than for patients in the TPC arm (2.17 months). For patients in Subgroup 2, median OS was 2.9 months longer for patients in the eribulin arm (13.0 months) than for patients in the TPC arm (10.1 months); whilst median PFS was 1.5 months longer for patients in the eribulin arm (3.6 months) than for patients in the TPC arm (2.1 months). The median number of cycles of eribulin in the EMBRACE trial was reported to be between five and six.

Most patients in the EMBRACE trial experienced at least one all-Grade adverse event (AE): 98.8% of patients in the eribulin arm and 93.1% in the TPC arm. Very common all-Grade AEs associated with eribulin included neutropenia (51.7%), asthenia/fatigue (53.7%), alopecia (44.5%), peripheral neuropathy (34.6%), arthralgia/myalgia (21.7%) and nausea (34.6%). Grade ≥3 AEs occurred more frequently in the eribulin arm than in the TPC arm of the trial (90.7% versus 59.5%). The most common Grade ≥3 AE for patients treated with eribulin was neutropenia (49.7%). Febrile neutropenia (4.2%) and neutropenia (1.8%) were the most frequently reported serious AEs associated with treatment with eribulin. There were no notable differences in AE frequencies between the EMBRACE trial safety and Subgroup 2 populations.

Additional evidence was provided from studies not identified via the systematic review:

- supportive 'real world' safety data were reported by the company from five observational studies: three audits of patients whose treatments were funded by the Cancer Drugs Fund (CDF) in England (n=208 across all three studies), and the EUFORIA-1 (n=104) and ERIBEX (n=258) studies which were carried out in Spain and France/Switzerland respectively. Patients included in the CDF audits had, on average, received ≥3 prior lines of chemotherapy for LABC/MBC whilst patients in the international studies had received four or five prior lines of chemotherapy for LABC/MBC (≥80% received previous treatment with capecitabine across the five studies). In most cases, the frequencies of key AEs (asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy and nausea) were lower than the frequencies reported for the EMBRACE trial safety population.

- health-related quality of life (HRQoL) data were derived from Study 301, another multi-centre, phase III, open-label, randomised parallel two-arm trial. Study 301 included patients who had received no more than two regimens for LABC/MBC; this study excluded patients who had been previously treated with capecitabine. Study 301 included 1102 patients, 554 patients randomised to eribulin and 548 patients randomised to capecitabine. The results from Study 301 patients who had received third-line treatment only show that treatment with eribulin does not have an adverse impact on HRQoL as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Over time, patients in both arms appeared to maintain or improve their baseline global health status/ quality of life.

## *1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted*

The ERG is satisfied with the clinical effectiveness systematic review process described in the company submission (CS) and is, therefore, confident that the EMBRACE trial is the only trial that is relevant to a review of TA250. The company's systematic review was only designed to find evidence for Subgroup 2 patients (since this is the population on which the cost effectiveness analysis is based) and not for all patients receiving ≥3 chemotherapy regimens for LABC/MBC. The ERG is not aware of additional randomised controlled trials (RCTs) that could have provided evidence for all patients receiving ≥3 chemotherapy regimens for LABC/MBC or for the Subgroup 2 population. Given HRQoL data were not collected in the EMBRACE trial, the ERG considers attempts to derive HRQoL data from other sources (e.g. Study 301) were appropriate. While HRQoL data from the EORTC QLQ-C30 questionnaire are provided for third-line patients in Study 301, patients had not received later lines of treatment in this trial and the comparator arm was capecitabine. Therefore, the generalisability of HRQoL data from Study 301 to all patients receiving ≥3 chemotherapy regimens for LABC/MBC or Subgroup 2 patients may be questioned.

Overall, the ERG is satisfied with the statistical approach employed by the company for the EMBRACE trial, with the exception of a lack of testing of the proportional hazards (PH) assumption. The ERG cautions that the approach taken by the company to calculate hazard ratios (HRs) is only valid if the relevant Kaplan-Meier (K-M) data are proportional to one another, i.e. the HRs are only reliable if the PH assumption holds.

The ERG notes that the baseline characteristics of patients in Subgroup 2 are broadly similar to the baseline characteristics of the ITT population and also that baseline characteristics appear to be well balanced across treatment groups. The main difference between the ITT and Subgroup 2 populations is that Subgroup 2 patients appear to be more heavily pre-treated: approximately 64% of Subgroup 2 patients had received four or more prior chemotherapy regimens (in any setting) compared with approximately 53% of all patients in the ITT population; also, approximately 65% of Subgroup 2 patients had received three or

more prior chemotherapy regimens in the LABC/MBC setting compared with approximately 57% of all patients in the ITT population.

The ERG considers that both the EMBRACE trial and Study 301 were generally well designed and conducted. The ERG agrees with the company's view that both trials were at low risk of bias.

Overall, the ERG considers that the findings from the EMBRACE trial demonstrate an improvement in median OS and median PFS for patients treated with eribulin versus those treated with TPC. This is true for both the ITT and the Subgroup 2 populations. However, the ERG notes that the only the ITT OS HR is reliable; all other HRs (Subgroup 2 OS and PFS for both ITT and Subgroup 2 populations) are derived from K-M data that are not proportional to one another.

The ERG also considers that the safety data from the EMBRACE trial and from 'real world' observational studies show that eribulin has an acceptable safety profile.

## *1.4 Summary of submitted cost effectiveness evidence*

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with eribulin with a chemotherapy agent of TPC. The model comprised three mutually exclusive health states: pre-progression or stable disease, post-progression or progressive disease, and dead. All patients enter the model in the stable health state and remain in this state until disease progression. The model time horizon is set at 5 years in the base case with monthly cycles. The model perspective is that of the UK NHS. Outcomes were measured in quality adjusted life years (QALYs), and both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE. Survival was estimated based on data from the EMBRACE trial. Utility values were mapped to EQ-5D values from the responses of patients in Study 301 completing the EORTC QLQ-C30 questionnaire. Resource use and costs were estimated based on information from the EMBRACE trial, published sources and clinical experts.

In the base case, eribulin generates more benefits than TPC [redacted] life years gained [LYG] and +[redacted] QALYs) at an increased cost of [redacted]. The company base case incremental cost effectiveness ratio (ICER) for eribulin versus TPC is £35,624 per QALY gained. The company carried out a range of deterministic sensitivity analyses. The parameter changes that had the effect of changing the base case ICER per QALY gained by more than 10% were decreasing the progressive disease utility from 0.679 to 0.496 (which increased the company's base case ICER by 31.7% to £46,912 per QALY gained) and adjusting the cost of eribulin by ±20% (which led to corresponding ±12.3% change to the company's base case ICER, i.e. £31,226 and £40,022 per QALY gained respectively).

The company's probabilistic sensitivity analysis (PSA) involved varying only a limited number of parameters. There is a 30% probability of treatment with eribulin being cost effective at a threshold of £30,000 per QALY gained and a 72% probability of it being cost effective at a threshold of £50,000 per QALY gained.

The company carried out six scenario analyses. Excluding the cost of drug wastage had the largest impact and lowered the ICER to £16,053 per QALY gained (a 54% reduction in the base case result).

### *1.5 Summary of the ERG's critique of cost effectiveness evidence*

The ERG considers that trial data are more reflective of patient experience than projective functions. However, the company has used projective functions to model patient OS and PFS experience over the whole model time horizon. The ERG presents results generated by using the available EMBRACE trial K-M data for OS and PFS directly in the model, and only using projective functions to model the OS experience of three patients who were still alive at the time of the final data-cut.

The ERG has serious doubts about the reliability of the PPS K-M data provided in response to a clarification request and, therefore, was unable to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression. However, OS and PFS estimates give strong support to a substantial gain in mean survival being experienced by some patients even after recorded disease progression and cessation of treatment with eribulin.

The ERG identified, and subsequently corrected, a number of issues relating to the way in which the company has costed drugs. Two logic errors were identified, one relating to the cost of vinorelbine and the other to the cost of administering eribulin. The ERG also identified issues with the body surface area (BSA) values used to calculate the acquisition cost of chemotherapy, a dose intensity multiplier that only had an affect when the company's alternative approach to calculating drug costs (i.e. without wastage) was applied, and an arbitrary dose capping measure. In addition, the company provided two approaches to estimating the cost of further lines of chemotherapy, both of which lead to anomalous results. The ERG has, therefore, provided results using a different approach to costing further lines of chemotherapy.

The ERG questions the appropriateness of the algorithm applied by the company to convert QLQ-C30 quality of life values to EQ-5D utility values. In addition, the ERG notes that the value used in the company model to represent the HRQoL of patients with stable disease (but not responding to treatment) is very similar to the value for progressed disease (0.69

versus 0.68) and considers this level of similarity to be implausible. The ERG has, therefore, generated cost effectiveness results using their preferred utility estimates.

Three further issues have been identified by the ERG. First, within the company model, costs and benefits are discounted on a continuous basis rather than annually in line with NHS budgeting and accounting years. Second, the method employed by the company to carry out PSA does not take into account uncertainty related to correlated values. Furthermore, drug costs are only varied in a deterministic manner. Third, the ERG does not consider that the company has explored parameter uncertainty sufficiently.

## *1.6 Summary of company's case for end of life criteria being met*

The company makes the following case for eribulin to be considered under NICE's end of life criteria:

- Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine, have a life expectancy of less than 24 months
- Data from the EMBRACE trial demonstrate that eribulin extends life by more than 3 months compared with TPC.

## *1.7 ERG commentary on end of life criteria*

The ERG agrees with the company that eribulin is a treatment that is indicated in patients with a short life expectancy. The ERG also considers that eribulin is likely to offer an extension to life of at least an additional 3 months compared to current NHS treatment; the ERG estimates a mean OS gain of 3.39 months (95% confidence interval 0.83 to 5.96 months) for patients treated with eribulin compared with patients treated with TPC although this does not achieve statistical significance due to the small trial population.

## *1.8 ERG commentary on the robustness of evidence submitted by the company*

### 1.8.1 Strengths

**Clinical evidence**

- The EMBRACE trial compared the efficacy and safety of eribulin with TPC, a comparator arm that reflects the real life choices faced by physicians and patients with an advanced stage of LABC/MBC
- Mature clinical effectiveness data are available (95% of patients have died)
- The EMBRACE trial is the only currently available source of good-quality clinical effectiveness evidence describing the use of treatments available to patients receiving ≥3 chemotherapy regimens for LABC/MBC.

**Cost effectiveness evidence**

- The availability of mature survival data allows a reliable assessment of the relative effectiveness of treatment with eribulin versus TPC for the Subgroup 2 population.

### 1.8.2 Weaknesses and areas of uncertainty

**Clinical evidence**

- HRQoL data were not available from the EMBRACE trial
- Although HRQoL data for third-line patients were available from Study 301, only 28% of all patients in this trial received study treatment as a third-line option for LABC/MBC. The majority of all patients in the ITT population included in the EMBRACE trial (including patients in Subgroup 2) had received a greater number of previous lines of treatment than those participating in Study 301. Study 301 also excluded patients previously treated with capecitabine (unlike the EMBRACE trial). Thus it is unclear if the available HRQoL data are generalisable to all patients receiving ≥3 chemotherapy regimens for LABC/MBC or to Subgroup 2 patients.

**Cost effectiveness evidence**

- No evidence has been provided to demonstrate the cost effectiveness of treatment with eribulin versus TPC for the ITT population
- Projective functions, rather than mature EMBRACE trial survival data, have been used within the company model to reflect patient PFS and OS experience. This has led to inaccurate estimates of the efficacy of eribulin versus TPC
- Within the company model, costs and benefits have been discounted continuously rather than annually
- The ERG has identified several issues relating to the methods employed by the company to estimate drug acquisition and administration costs
- The company has used an implausibly high post-progression utility value
- The exploration of parameter uncertainty undertaken by the company is insufficient.

## *1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG*

The ERG implemented nine individual corrections/modifications to the company's model. When these changes are implemented individually for the comparison of the cost effectiveness of treatment with eribulin versus TPC for the Subgroup 2 population, they both increase and decrease the size of the company's base case ICER per QALY gained. The three most influential ERG changes are the revised estimate of the cost of eribulin treatment (base case ICER change: +£12,575), the choice of utility value for the progressive disease health state (base case ICER change: +£11,288), and the method used to cost subsequent lines of treatment (base case ICER change: +£9,811). The combined effect of all of the ERG changes yields an ICER of £66,043 per QALY gained.

In conclusion, the ERG considers that the company's base case ICER substantially underestimates the size of the most probable ICER per QALY gained (by £30,418) for the comparison of treatment with eribulin versus TPC in patients with LABC/MBC whose disease

has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine.

# 2 CONTEXT

## *2.1 Original NICE guidance TA250 (2012)*

In April 2012, the National Institute for Health and Care Excellence (NICE) published guidance on the use of eribulin for the treatment of locally advanced or metastatic breast cancer (LABC/MBC).[1] At the time, eribulin was indicated for the treatment of patients with LABC/MBC who had progressed after at least two chemotherapy regimens for advanced disease. A year earlier, in April 2011, eribulin was first made available to some NHS patients via regional panels of the Cancer Drugs Fund (CDF).

## *2.2 New licence for eribulin (2014)*

In July 2014, the European Medicines Agency (EMA) granted an extension to the previous indication for eribulin.[2] This enabled eribulin to be used earlier in the treatment pathway. The new indication for eribulin is for the treatment of adult patients with LABC/MBC who have progressed after one or more chemotherapy regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless these treatments were not suitable.

## *2.3 Current single technology appraisal (2016)*

In April 2016, NICE issued a scope for the appraisal of eribulin within its (new) indication for the treatment of adults with breast cancer who have received one or more chemotherapy regimens for locally advanced or metastatic disease.[3] According to information published on the NICE website,[4] the aim of the this new single technology appraisal (STA) was to fully update the previous guidance (TA250). In the company submission (CS)[5] for this appraisal the company interpreted the new remit to consist of two elements (CS, p10):

- LABC/MBC – following one prior chemotherapy (appraisal of new indication)
- LABC/MBC – following two prior chemotherapies (review of TA250).

The company relates these two elements to two populations, each of which is supported by evidence from different trials:

- Subgroup 1:
    - **Population**: human epidermal growth factor receptor 2 (HER2)-negative patients with LABC/MBC whose disease has progressed after one prior chemotherapy regimen in the advanced setting
    - **Main evidence source**: Study 301,[6] a phase III randomised controlled trial (RCT) in which treatment with eribulin is compared with treatment with capecitabine.

- Subgroup 2:
    - **Population**: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated).
    - **Main evidence source**: the phase III EMBRACE trial[7] in which treatment with eribulin was compared with Treatment of Physician's Choice (TPC)

The company has provided only one economic model but, within that model, the two subgroups are considered separately, with a distinct 'model' being run for each subgroup and cost effectiveness results being presented separately.

Following discussions between the company, NICE and the Evidence Review Group (ERG), it was agreed (on 20 July 2016) that the evidence for the two subgroups should be considered separately, i.e. as two separate STAs. **This current STA focuses only on reviewing TA250, in which eribulin was considered as a third-line (or later) treatment option for patients with LABC/MBC**, i.e. patients receiving ≥3 chemotherapy regimens for LABC/MBC which includes those previously treated with capecitabine (Subgroup 2) as well as those who have not previously been treated with capecitabine (the remainder of the EMBRACE trial ITT population).

## *2.4 Summary of evidence reviewed for TA250*

To inform the original STA (TA250), the company presented evidence to support the clinical and cost effectiveness of eribulin using data from region 1 of the EMBRACE trial (i.e. from patients in North America, Western Europe and Australia). Patients participating in the EMBRACE trial were recruited from three different regions and the company argued that clinical practice in region 1 was likely to be more reflective of UK practice than clinical practice in the other two regions.

The company presented evidence for the effectiveness of treatment with eribulin versus TPC as a whole, as well as versus three (vinorelbine, capecitabine and gemcitabine) of the numerous individual agents that physicians chose to prescribe. At the first Appraisal Committee (AC) meeting, the AC considered that it was more appropriate to use data from all patients rather than restricting the evidence to only those patients in region 1 since the marketing authorisation for eribulin was based on the results of the overall EMBRACE population rather than on any subgroup results. Furthermore, the AC noted that analysis carried out by the ERG showed that mean overall survival (OS) did not differ by region, whilst UK practice differed considerably from some areas included in region 1. The company, therefore, provided additional evidence and this evidence was the focus of discussions that informed the content of the final appraisal determination (FAD) document.

There were two main reasons for these two foci:

1. "The … [EMBRACE] trial should be evaluated as a whole as this was how the study had been designed and powered" (FAD 4.4)[1] and
2. "… a major stratification factor in the EMBRACE trial was pre-treatment with capecitabine (73.4% of patients) and … this was potentially relevant to clinical practice" (FAD 4.11).[1]

The AC's conclusions about the clinical and cost effectiveness of eribulin versus TPC for all patients and eribulin versus vinorelbine for patients previously treated with capecitabine (i.e. Subgroup 2) are presented in the FAD. The FAD includes the following guidance:

> *"Eribulin is not recommended, within its licensed indication, for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease"* (FAD 1.1).[1]

In the current STA, the company also highlights five key conclusions that the AC reached with regard to appropriate evidence and gaps in the evidence relating to the safety of eribulin, health-related quality of life (HRQoL) associated with eribulin, the focus on patients previously treated with capecitabine, modelling OS and estimating and incorporating drug costs in the model. The company states that it has attempted to address all of these issues in the current CS.

## *2.5 Critique of company's description of underlying health problem*

The company's brief description of the underlying health problem is presented in Sections 1.3 and 3 of the CS. Key points from these sections of the CS are reproduced (as bulleted items) in Box 1. The ERG considers that the company's description presents an accurate summary of the underlying health problem.

Box 1 Summary of company's description of underlying health problem

**Incidence and survival**

- Breast cancer is the most common malignancy in the UK; it accounts for 15% of all new cases and the lifetime risk of developing breast cancer for a woman is 1 in 8
- The risk of developing breast cancer is strongly correlated with age; 80% of cases in the UK occur in women aged 50 years and over
- Locally advanced breast cancer or metastatic breast cancer (LABC/MBC) is the most advanced form of breast cancer, where the cancer is no longer localised to the breast and has spread to other parts of the body, commonly the lungs, liver, brain and bone
- Although few patients are diagnosed with MBC at the outset (around 5%) as many as 35% of women diagnosed with early breast cancer will eventually progress to or relapse with LABC/MBC
- There is currently no cure for MBC and the long-term prognosis is poor
- The proportion of patients responding to chemotherapy declines through successive lines of treatment
- As reported in the NICE assessment report for lapatinib and trastuzumab, the average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18 to 24 months for those receiving chemotherapy

**Health-related quality of life**

- Symptoms can be severe including cancer-related fatigue and uncontrolled local disease, along with further complications relating to the organ(s) to which the cancer has spread
- Overall, quality of life is poor in patients with MBC. MBC patients have lower scores than non MBC in all of the functioning subscales of the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire

Source: CS, Sections 1.3 and 3

## *2.6 Critique of company's overview of current service provision*

The company's overview of current service provision is presented in Sections 1.3, 2.4 and 3 of the CS. Key points from these sections are reproduced (as bulleted items) in Box 2. Overall, the ERG agrees with the company's overview of current service provision. The ERG notes that, as a result of the 2014 licence extension, eribulin is indicated for the treatment of adult patients with LABC/MBC who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. For these patients, clinical advice to the ERG is that eribulin is most likely to be considered as an alternative to treatment with either vinorelbine monotherapy or capecitabine monotherapy.

The company considers that patients who have received at least two prior chemotherapy regimens for LABC/MBC would most likely have received capecitabine prior to receiving eribulin. Indeed, as highlighted in Box 2, the company cites data from independent audits which show that more than 80% of patients received prior capecitabine when prescribed eribulin (as a third-line or later treatment) via the CDF.

Information in Box 2 also highlights that, within the current NICE guideline for advanced breast cancer (CG81),[8] recommendations are only made for treatment up to, and including, third-line therapy. Beyond third-line there is no clear standard of care.

Box 2 Summary of company's overview of current service provision

- LABC/MBC is generally managed by a multi-disciplinary healthcare team in tertiary, secondary and primary care
- The aim of treatment for LABC/MBC is to prolong life, without adversely affecting the patient's quality of life
- The chemotherapeutic agents with the best efficacy in breast cancer, the anthracyclines and taxanes, are typically used at earlier stages of the disease, leaving many LABC/MBC patients anthracycline and taxane-resistant, and thereby limiting the number of treatment options at this stage of disease
- Despite recent improvements in the treatment of MBC, there is still no consensus regarding the optimal standard of care for women requiring therapy after initial taxane and anthracycline treatment
- Based on the NICE clinical guideline for advanced breast cancer, following anthracycline treatment, systemic chemotherapy should be offered in the following sequence:
    - First-line: single-agent docetaxel [i.e. a taxane]
    - Second-line: single-agent vinorelbine or capecitabine
    - Third-line: single agent vinorelbine or capecitabine (whichever was not used as second-line treatment)
- Whilst the NICE clinical guideline clearly defines vinorelbine monotherapy and capecitabine monotherapy as options for second-line treatment and beyond, in clinical practice, as indicated above, it is apparent that for patients with LABC/MBC, particularly at this advanced point in their treatment, numerous types of treatment may be used. The choice of treatment will depend on factors including HER2-status, prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, the patient's quality of life and performance status
- Recently published data from independent audits undertaken at the Royal Marsden Hospital, Christie Hospital NHS Foundation Trust and Imperial College Healthcare NHS Trust showed that more than 80% of patients had received prior capecitabine when prescribed eribulin via the Cancer Drugs Fund
- The tolerability of current LABC/MBC treatment varies; chemotherapy agents can be particularly toxic and are recognised to be the most burdensome aspect of cancer management for patients
- Side effects of chemotherapy commonly include peripheral neuropathy, alopecia, mucositis, nausea, vomiting, increased infection, and fatigue. These can adversely affect a patients' quality of life, be costly to manage and lead to early discontinuation of a particular therapy in a significant number of patients, thereby impacting on overall treatment outcomes
- Other issues relating to current practice include the inconvenience to the patient and the treating healthcare professional, and the level of resource use required for administration:
    - The majority of chemotherapy regimens require intravenous (IV) administration and vary in their infusion times (e.g. paclitaxel is administered over 3 hours). Patients may experience difficulties with venous access as a result of multiple prior therapies, while long infusion times can be inconvenient and increase the burden to the patients' lives.
    - Variability exists in frequency of dosing schedules (e.g. vinorelbine requires weekly administration). The lack of consistency and the impact that missing doses may have on clinical outcomes mean that patient outcomes may also be inconsistent.
    - Many IV chemotherapy regimens require reconstitution or dilution before administration (e.g. gemcitabine, vinorelbine), increasing the burden on healthcare resources, and potentially leading to dosing errors. Vinorelbine is also a vesicant
    - Premedication with steroids and/or antihistamines to prevent hypersensitivity reactions during administration is necessary with many chemotherapeutic agents (e.g. docetaxel, paclitaxel). This increases the time required for treatment administration as well as the overall cost of treatment and adds to the potential drug-related adverse effects that the patient may experience

Source: CS, Sections 1.3, 2.4 and 3

## 2.7 Number of patients potentially eligible for eribulin

The company has estimated that the total number of patients in England and Wales who are potentially eligible to receive treatment with eribulin is 2044. Of these, it is estimated that 1500 will be eligible to receive eribulin following treatment with capecitabine (Subgroup 2). As shown in Table 1, the company's estimates are based on prevalence data.

Table 1 Company estimate for patients potentially eligible for treatment with eribulin

| Population | Number | % | Source |
|---|---|---|---|
| Population of England and Wales | 57,408,700 | | Office for National Statistics mid-year estimate, 2014[9] |
| Prevalence of breast cancer | 80,372 | 0.14 | Cancer Mpact database, Kantar Health[10] |
| Prevalence of metastatic breast cancer | 5940 | 7.39 | Cancer Mpact database, Kantar Health[10] |
| Patients receiving first-line chemotherapy | 5940 | 100.00 | Company assumption |
| Patients receiving second-line chemotherapy | 3883 | 65.37 | Cancer Mpact database, Kantar Health[10] |
| Patients on third-line chemotherapy | 2044 | 52.64 | Cancer Mpact database, Kantar Health[10] |
| Patients treated following treatment with capecitabine (Subgroup 2) | 1500 | 73.40 | EMBRACE[7] |

Source: CS, Table 86

The ERG notes that alternative estimates can be derived from incidence data. As shown in Table 2, when estimates of the numbers of patients in the ITT and Subgroup 2 populations eligible to receive eribulin are calculated using incidence rather than prevalence data, the resultant figures are similar (ITT population: 2149 patients and Subgroup 2 population: 1578 patients).

Table 2 ERG estimate for patients potentially eligible for treatment with eribulin

| Population | Number | % | Source |
|---|---|---|---|
| Breast cancer incidence in England and Wales | 44,683 | | Cancer Research UK[11] |
| Incidence with known stage of disease | 40,101 | 84.10 | Cancer Research UK[12] |
| Incidence of patients with Stage III to IV disease | 6246 | 13.10 | Cancer Research UK[12] |
| Patients receiving first-line chemotherapy | 6246 | 100.00 | Company assumption |
| Patients receiving second-line chemotherapy | 4083 | 65.37 | Cancer Mpact database, Kantar Health[10] |
| Patients on third-line chemotherapy | 2149 | 52.64 | Cancer Mpact database, Kantar Health[10] |
| Patients treated following treatment with capecitabine (Subgroup 2) | 1578 | 73.40 | Cancer Mpact database, Kantar Health[10] |

However, the ERG questions the validity of the company assumption that 100% of patients receive first-line chemotherapy. In the original STA for eribulin (TA250), the ERG noted that the company estimated the proportion to be 61.8% based on market share data for the third quarter of 2010.[13] Applying this estimate reduces the prevalence and incidence based estimates to 1263 and 1328 respectively for the EMBRACE trial ITT population and 927 and 975 respectively for Subgroup 2 patients. Clinical opinion received by the ERG is that a more reasonable estimate for patients receiving first-line chemotherapy may be approximately 75%. Assuming the proportion of patients receiving first-line chemotherapy to be 75% changes the estimated patient numbers to between 1533 (company) and 1612 (ERG) for all patients receiving ≥3 chemotherapy regimens for LABC/MBC and to between 1125 (company) and 1183 (ERG) for Subgroup 2 patients.

# 3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem described by the company in the CS in relation to the final scope issued by NICE is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 1.1 to Section 3.7). **As noted in Section 2.3, the CS provides information relating to two subgroups of patients; however, this ERG report only considers the information provided by the company that facilitates a review of TA250.**

Table 3 Final NICE scope and company's decision problem

| Parameter | Final scope issued by NICE | Decision problem addressed in the CS |
|---|---|---|
| Population | Adults with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (anthracycline and a taxane, unless these treatments were not suitable) | Clinical and cost effectiveness evidence is presented for Subgroup 2 patients: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated). This was one of two populations on which the Appraisal Committee finally focussed on in TA250<br><br>Clinical effectiveness evidence is also presented for the broader population of patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease (but who have not received prior capecitabine). This was the other population on which the Appraisal Committee finally focussed on in TA250 |
| Intervention | Eribulin | As per scope |
| Comparator (s) | • Vinorelbine<br>• Capecitabine<br>• Gemcitabine | Clinical effectiveness: Treatment of Physician's Choice (TPC), including:<br>• Vinorelbine<br>• Capecitabine<br>• Gemcitabine<br>• Anthracyclines (doxorubicin)<br>• Taxanes (paclitaxel and docetaxel)<br><br>Clinical effectiveness and base case cost effectiveness: Treatment of Physician's Choice (TPC), including:<br>• Vinorelbine<br>• Gemcitabine<br>• Anthracyclines (doxorubicin)<br>• Taxanes (paclitaxel and docetaxel)<br><br>Cost effectiveness scenario analysis: 57% of population received vinorelbine and 43% received gemcitabine |

| Parameter | Final scope issued by NICE | Decision problem addressed in the CS |
|---|---|---|
| Outcomes | • Overall survival<br>• Progression-free survival<br>• Response rates<br>• Adverse effects of treatment<br>• Health related quality of life | As per scope for all patients in the EMBRACE trial<br><br>Health-related quality of life data are derived from an alternative trial (Study 301)<br><br>The only endpoints reported for Subgroup 2 patients are:<br>• Overall survival<br>• Progression-free survival<br>• Adverse effects of treatment (during the clarification process) |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>The availability of any patient access schemes for the intervention or comparator technologies will be taken into account | The economic evaluation utilised patient-level data from the EMBRACE trial. 5-year survival data from this trial were very close to being complete and the company therefore set the base case time horizon to 5 years. Cost effectiveness results from scenario analyses considering 10- and 20-year time horizons were also provided<br><br>Costs were considered from an NHS perspective<br><br>A Patient Access Scheme for eribulin has been approved by the Department of Health and this cost has been used in the cost effectiveness analyses |
| Subgroups to be considered | If the evidence allows, consideration will be given to subgroups according to HER2 status, oestrogen receptor and line of treatment<br>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator | Subgroup 2 patients are representative of patients in current clinical practice in England as observed through the usage of eribulin obtained via the Cancer Drugs Fund (CDF). Recently published data from three audits undertaken in England show that 80% or more of patients who had obtained eribulin via the CDF had received prior capecitabine |
| Other considerations | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. | Since the licence for eribulin has been updated to enable eribulin to be used earlier in the treatment pathway, and since the current STA is a review of TA250, all patients receiving ≥3 chemotherapy regimens for LABC/MBC and Subgroup 2 patients constitute subgroups of the licensed population. For these heavily pre-treated patients, the company considers eribulin should be considered using NICE's end of life criteria |

Source: Final scope issued by NICE and CS, adapted from Table 1

## 3.1 Population

The company presents clinical effectiveness evidence for all patients in the EMBRACE trial, i.e. patients with LABC/MBC whose disease has progressed after at least two (and a maximum of five) prior chemotherapeutic regimes for advanced disease (the ITT population). The company also presents clinical effectiveness evidence for patients in the EMBRACE trial whose previous treatment had included capecitabine (if indicated) as well as both an anthracycline and a taxane. This subgroup is referred to in the CS (and in this ERG report) as 'Subgroup 2'. Subgroup 2 was pre-defined and comprises 73% of the EMBRACE trial population. In the CS, cost effectiveness evidence is only presented for Subgroup 2 patients. A summary of detail relation to populations addressed in this STA is presented in Table 4.

Table 4 Summary of populations addressed in the current single technology appraisal

| Population | Clinical effectiveness | Cost effectiveness |
|---|---|---|
| Patients receiving ≥3 chemotherapy regimens for LABC/MBC<br><br>(Original indication for eribulin) | All patients in the EMBRACE trial, i.e. the ITT population (AE results calculated for the safety population) | The company did not carry out any cost effectiveness analyses for this population |
| Subgroup 2: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated) | Pre-specified subgroup in the EMBRACE trial<br><br>These patients comprises 73% of the EMBRACE trial population | This population is the focus of the cost effectiveness analyses |

AE=adverse events; ITT=intention-to-treat, LABC/MBC=locally advanced breast cancer/metastatic breast cancer

The whole EMBRACE trial population (and Subgroup 2) is a subset of the population specified in the final scope issued by NICE (the population for whom eribulin is now indicated). However, the whole trial population is consistent with the previous indication for eribulin. The whole trial population and Subgroup 2 are the same populations that were the final focus of the AC during TA250. The ERG, therefore, considers that the company presents appropriate clinical effectiveness evidence for a review of TA250. The ERG also notes that the whole EMBRACE trial population is also reflective of the patient population that has been treated with eribulin via the CDF in England to date.

## 3.2 Intervention

Eribulin is a first-in-class anti-neoplastic agent belonging to the halichondrin class of drugs. Anti-cancer effects are exerted via a tubulin-based antimitotic mechanism leading to G2/M cell cycle arrest, disruption of mitotic spindles and, ultimately, apoptotic cell death following prolonged mitotic blockage.[14,15] Eribulin monotherapy is administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle. The company notes that pre-medication (antihistamine or steroids) to prevent hypersensitivity reactions is not routinely required prior to injection with eribulin, which sets treatment with eribulin apart from many intravenous (IV)

chemotherapeutic agents. The company also states that, for patients treated with eribulin, the location of care, level of staff usage, cost of administration, frequency and type of monitoring and tests are all of a similar magnitude to other IV chemotherapeutic agents currently used in clinical practice.

## 3.3 Comparators

The comparators specified in the final scope issued by NICE are vinorelbine, capecitabine and gemcitabine. As noted in Section 2.6 of this ERG report, NICE recommend that single agent vinorelbine or single agent capecitabine should be prescribed second- or third-line (if the second-line treatment is vinorelbine then the third-line treatment would be capecitabine and vice versa).[8] As noted in Section 2.6, beyond third-line, there is no standard of care. Given this, using TPC as the comparator in the EMBRACE trial appears reasonable. The TPC used in the trial included (but was not limited to) chemotherapy (93.7%) and hormonal therapy (3.5%). The most common agents (59.4% of all TPC agents, 63.4% of all chemotherapy agents) were the comparators listed in the final scope issued by NICE: vinorelbine, capecitabine and gemcitabine. The other most common agents were anthracyclines (~10%) and taxanes (~15%).

In the EMBRACE trial, patients had to have been previously treated with anthracyclines and taxanes. The company notes that, in clinical practice, some patients are re-challenged with these agents and hence considers that these agents are appropriate for use in the TPC arm. The ERG agrees with the company that, in clinical practice, due to a lack of alternative treatments, taxanes are often used again at this late stage in the treatment pathway. Clinical advice to the ERG is that re-challenge with anthracyclines is uncommon due to dose dependent cardiac toxicity associated with this this type of agent.

In producing its guidance for TA250, the AC considered that TPC was an appropriate comparator for all patients receiving ≥3 chemotherapy regimens for LABC/MBC and that vinorelbine was an appropriate comparator for the Subgroup 2 population. The ERG considers that whilst vinorelbine is an appropriate comparator for Subgroup 2 patients, using data for only one of the TPC agents results in a reduction in the overall volume of admissible EMBRACE trial data and increases the uncertainty around clinical and cost effectiveness results. Given that the ERG also considers that other agents are appropriate comparators at this stage of the treatment pathway, the use of TPC as a comparator for Subgroup 2 patients in the current appraisal appears to be both pragmatic and justified.

## 3.4 Outcomes

The outcomes specified in the final scope issued by NICE are OS, progression-free survival (PFS), response rates, adverse events (AEs) and HRQoL; these are standard outcomes

used in oncology clinical trials and are the most important outcome measures for this appraisal.

Clinical evidence from the EMBRACE trial is reported in the CS for patients receiving ≥3 chemotherapy regimens for LABC/MBC for all outcomes specified in the final scope issued by NICE, with the exception of HRQoL data. HRQoL data are only available from a subgroup of patients participating in Study 301 who received treatment with either eribulin or capecitabine. For patients in Subgroup 2, data from the EMBRACE trial are only presented in the CS for OS and PFS; information on AEs was provided during the clarification process; HRQoL data for this population have been derived by the company from Study 301.

## *3.5 Economic analysis*

Cost effectiveness evidence is only presented for the Subgroup 2 population. No cost effectiveness evidence is presented for patients receiving ≥3 chemotherapy regimens for LABC/MBC who are capecitabine naive. As specified in the final scope issued by NICE, the company expresses the cost effectiveness of treatments in terms of the incremental cost per QALY gained. In the base case, outcomes are assessed over a 5-year time horizon and 10- and 20-year time horizons are considered in scenario analyses. Costs are considered from an NHS perspective. A simple Patient Access Scheme offering a straight discount to the list price of eribulin was formally agreed with the Department of Health on 14 January 2016. This cost is used in the company's cost effectiveness analyses.

## *3.6 Subgroups*

As described in Section 2.3 and Section 1.1, the information in the CS focuses specifically on Subgroup 2: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated).

## *3.7 Other considerations*

Since the licence for eribulin has been updated to allow eribulin to be used earlier in the treatment pathway, and since the current STA is a review of TA250, all patients receiving ≥3 chemotherapy regimens for LABC/MBC and Subgroup 2 patients constitute subgroups of the licensed population. For these heavily pre-treated patients, the company considers that the cost effectiveness of eribulin should be appraised using NICE's end of life criteria.

# 4 CLINICAL EFFECTIVENESS

The company originally conducted two systematic reviews, one to find evidence for the Subgroup 1 population and the other to find evidence for the Subgroup 2 population. Only the latter is relevant to this appraisal (see Section 2 of this ERG report) and it is, therefore, only detail relating to the latter that has been summarised and critiqued in this Section.

## *4.1 Methods*

Overall, despite the lack of some detail regarding the methods (see Sections 4.1.1 to 4.1.4 of this ERG report), the ERG is satisfied with the clinical effectiveness systematic review process as described in the CS. The ERG considers that the company's approach to evidence synthesis (see Section 4.1.5 of this ERG report) is appropriate.

### 4.1.1 Literature search methods

The CS adequately describes the search strategies used to identify relevant studies relating to the use of eribulin for the treatment of patients with LABC/MBC after chemotherapy. The company conducted a systematic search for RCT evidence. Separate searches were conducted for the retrieval of cost effectiveness studies (see Section 5.1 and 5.2 of this report).

Full details of the search terms used to locate clinical evidence are reported in the CS (Section 4.1 and Appendix 2). The company states that they searched the following databases: Medline (via PubMed), Embase (via Scopus) and The Cochrane Library. The date of the searches (23 December 2015) and the full date span (1 January 2009 to 30 November 2015) are appropriately reported by the company (CS, Appendix 2).

The company also conducted hand searches of four conference sites on 23 December 2015: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Association for Cancer Research (AACR) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). One clinical trial registry (clinicaltrials.gov) was searched (12 February 2016) as was the company's own clinical trial database (date not reported).

The ERG considers that the search terms used by the company were relevant for the databases searched. The use of free text only was appropriate as the databases that were searched did not have a Medical Subject Headings search function. Whilst Scopus does not include all references that are included in Embase, since the company also searched its clinical trial database for all completed studies from the eribulin clinical trial programme, the ERG is confident that all relevant studies have been identified.

In summary, the ERG is confident that the company's literature search for evidence for clinical effectiveness will have identified all relevant RCTs.

### 4.1.2 Eligibility criteria

The CS provides a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies. These are described in Table 5. Two reviewers independently undertook study selection in two stages:

- Stage 1 – review of abstracts
- Stage 2 – review of full text papers.

Table 5 Inclusion and exclusion criteria for treatment evidence for Subgroup 2 patients

| Parameter | Inclusion | Exclusion |
|---|---|---|
| Population | Adult patients AND<br>[MBC OR<br>Advanced breast cancer (ABC)] AND<br>AND 3L+ | Non-human OR<br>Children OR<br>Adolescents OR<br>Males OR<br>Studies with a unique focus on patients from outside Europe/USA were excluded |
| Intervention | Eribulin (monotherapy) | All other treatments or combinations |
| Comparator | Any | |
| Outcomes | PFS, OS (median and per cent survival at 1 year), ORR, TTR, duration response, TTP, adverse events | All others |
| Study design | RCT (phase II, III or IV) regardless of design (parallel, crossover, open label, single or double blinded) OR<br>Meta-analysis OR<br>Systematic Reviews | Editorials OR Notes OR<br>Comments OR RWE OR Letters OR<br>Other Reviews OR<br>Abstracts without full paper available<br>OR Phase I studies |
| Language | English | Non-English studies |

ABC=advanced breast cancer; MBC=metastatic breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; RWE=real world evidence; TTP=time to progression; TTR=time to response
Source: CS, Table 6

During both stages, publications not meeting the stated inclusion criteria were excluded and listed alongside the reason for exclusion. Where one reviewer included a study and the other did not, the full text paper was examined and was reviewed by both reviewers until agreement was reached.

The ERG notes that the eligibility criteria applied by the company in Table 5 enabled reviewers to exclude studies based on trial outcomes. This could, theoretically, introduce outcome selection bias[16] although the ERG also notes that as a wide range of outcomes were specified there was no need for included studies to report all outcomes and therefore, including or excluding studies based on outcomes is unlikely to be an important issue with regard to bias. However, the eligibility criteria did not include HRQoL as an outcome,

meaning that any studies that only reported HRQoL would have be excluded. Given the importance of HRQoL as a trial outcome, this would have been a major limitation had the company not also conducted a separate search for HRQoL studies. This literature search is described in Appendices to the ERG report, Section 11.1. As with the clinical effectiveness review, two reviewers independently undertook study selection in two stages. The eligibility criteria are described in Appendix 2 to the CS (reproduced in Appendices to this ERG report, Section 11.1).The same process for including or excluding studies was employed for the literature search for HRQoL studies as for the systematic review for clinical effectiveness.

### 4.1.3 Data extraction

After applying the eligibility criteria to the full texts, all papers meeting the inclusion criteria were retained for data extraction. The methods used for data extraction are not specified in the CS.

### 4.1.4 Quality assessment methods

A risk of bias assessment of RCTs included in the systematic review of clinical effectiveness was undertaken by the company using the method recommended by NICE.[17] It is, however, unclear whether this was completed by one reviewer, or independently by two reviewers.

### 4.1.5 Approach to evidence synthesis

The company's literature search led to the identification of only one RCT that was considered to be directly relevant to the decision problem (the EMBRACE trial). With the inclusion of only one relevant study, it was not possible for the company to carry out a meta-analysis.

The EMBRACE trial includes a population that is wider than the Subgroup 2 population and data from the wider population have been presented in the CS.

Since the investigators of the EMBRACE trial did not collect HRQoL data, the company appropriately sought and presented HRQoL evidence from other sources. The relevance of the HRQoL evidence to the decision problem for this STA is explored in Section 4.8.6 of this ERG report.

## *4.2 Identified studies in the systematic review*

The search conducted by the company identified nine relevant citations[7,18-25] for possible inclusion in its systematic review. All of these focus on the EMBRACE trial and include the clinical study report (CSR),[23] the updated CSR[22] and the full published paper from 2011.[7] The additional six citations[18-21,24,25] are two conference abstracts,[24,25] subsequently published

in full,[7] an additional updated analysis of OS and PFS for Subgroup 2 patients[18,22] and three conference abstracts[19-21] providing results from retrospective subgroup analyses.

An appropriate PRISMA[26] flow diagram, describing the review process was provided by the company (CS, Figure 6). The company listed all citations that were excluded from the review (at Stage 1 or Stage 2) in Appendix 2 to the CS. This list includes the following publications describing additional RCT data for the clinical effectiveness of eribulin in a broader patient population:

- Study 301,[6] a phase III RCT comparing eribulin with capecitabine as first-, second-, or third-line therapy for the treatment of LABC/MBC
- A pooled analysis[27] of Study 301 and the EMBRACE trial
- A phase II RCT designed primarily to assess safety (peripheral neuropathy) in patients with LABC/MBC (defined as locally recurrent or MBC).[28]

In Study 301, patients had not been pre-treated with capecitabine. Furthermore, only 28% of patients in Study 301 received third-line chemotherapy for LABC/MBC and no patient received more than third-line treatment. Not all patients were pre-treated with capecitabine and not all patients were receiving ≥3 chemotherapy regimens for LABC/MBC in the pooled analysis (the proportions being 30.0% and 56.6% respectively). Similarly, not all patients in the phase II trial had been pre-treated with capecitabine or received two or more lines of chemotherapy for LABC/MBC; 61.4% had received prior capecitabine and, while patients were required to have had prior taxane therapy and at least one prior cytotoxic chemotherapy for LABC/MBC, it is unclear how many patients had received two previous lines of therapy for LABC/MBC (although 32.7% had received three or more previous chemotherapy regimens in *any* setting). More importantly, the comparator in the phase II trial (Ixabepilone) is not relevant to the current decision problem.

The ERG is, therefore, confident that the EMBRACE trial is the only trial that provides evidence of the clinical effectiveness of eribulin for the Subgroup 2 population.

The only study identified by the company from its HRQoL evidence literature search was a publication by Greenhalgh et al.[29] The company note that this paper summarises the NICE STA (TA251) conducted in 2011 for which "the company extracted HRQoL data from the published literature, specifically Lloyd et al.[30] As relevant patient reported outcomes are now available for inclusion in this submission, these values are no longer needed, although they have been assessed in the deterministic sensitivity analysis" (CS, p158). The relevant patient reported outcomes referred to are HRQoL outcomes from Study 301.

## 4.3 Summary of trial characteristics and methodology

A summary of the characteristics of the EMBRACE trial and Study 301 (since it was used to as the source of HRQoL data) is provided in Table 6. Both trials were multi-centre, phase III, open-label, RCTs.

The primary objective of the EMBRACE trial was to evaluate the OS of patients treated with eribulin versus TPC in patients with LABC/MBC who had previously received two to five prior chemotherapy regimens. Patients were randomised in a 2:1 ratio to receive either eribulin or TPC, and randomisation was stratified according to geographical region, HER2 status, and prior treatment with capecitabine. The selection of the TPC agent took place prior to randomisation. TPC included (but was not limited to) chemotherapy (vinorelbine, capecitabine, gemcitabine, anthracyclines and taxanes were all permitted) and hormonal therapy.

The primary objective of Study 301 was to evaluate the OS and PFS for patients with LABC/MBC who had previously received no more than three prior chemotherapy regimens. However, only data from the secondary endpoint, HRQoL, were considered relevant to the current STA. Patients were randomised in a 1:1 ratio to receive either eribulin or capecitabine. Randomisation was stratified according to geographical region and HER2 status.

Patients in both trials were required to have been previously treated with an anthracycline and a taxane and, for the most part, eligibility criteria were similar in the two trials. However, unlike the EMBRACE trial, Study 301 excluded patients previously treated with capecitabine and patients were not required to have received previous treatment for LABC/MBC; rather, patients in Study 301 were required to have received no more than two regimens for LABC/MBC. In contrast, in the EMBRACE trial, patients were required to have received at least two regimens for LABC/MBC. Patients in the EMBRACE trial were also permitted to have received prior capecitabine, unlike in Study 301.

Table 6 Summary of the EMBRACE trial and Study 301 characteristics

| Parameter | Description | |
|---|---|---|
| | **EMBRACE trial** | **Study 301** |
| Intervention and comparator | Eribulin (N=508, randomised)<br>Eribulin administered as an IV infusion of 1.23mg/m$^2$ (equivalent to 1.4mg/m$^2$ eribulin mesilate) over 2 to 5 minutes on days 1 and 8 of a 21 day cycle<br>TPC (N=254, randomised)<br>The selection of the TPC agent took place prior to randomisation | Eribulin (N=554, randomised)<br>Eribulin administered as an IV infusion of 1.23mg/m$^2$ (equivalent to 1.4mg/m$^2$ eribulin mesilate) over 2 to 5 minutes on days 1 and 8 of a 21 day cycle<br>Capecitabine (N=548, randomised)<br>Capecitabine 1250mg/m$^2$ administered orally twice daily in two equal doses on days 1 to 14, every 21 days |
| Eligibility criteria for participants | • Patients previously treated with 2 to 5 chemotherapy regimens, including a taxane and an anthracycline; at least two regimens had to have been given for LABC/MBC<br>• Resolution of all chemotherapy or radiation-related adverse events to Grade 1 severity or lower, except for stable sensory neuropathy to Grade ≤2 and alopecia<br>• ECOG PS 0 to 2<br>• Life expectancy of ≥3 months<br>• Adequate renal, bone marrow and liver function, as determined by laboratory tests, based on pre-specified values | • Patients previously treated with up to 3 chemotherapy regimens, including a taxane and an anthracycline; no more than two regimens had to have been given for LABC/MBC<br>• Resolution of all chemotherapy or radiation-related adverse events to Grade 1 severity or lower, except for stable sensory neuropathy to Grade ≤2 and alopecia<br>• ECOG PS 0 to 2<br>• Life expectancy of ≥3 months<br>• Adequate renal, bone marrow and liver function, as determined by laboratory tests, based on pre-specified values<br>• Prior treatment with capecitabine was not permitted |
| Location | 135 secondary care centres in 19 countries (including UK) | 210 secondary care centres in 24 countries |
| Permitted and disallowed concomitant medications | Medications included: any medication considered necessary for patient's welfare not expected to interfere with evaluation of study<br>Primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement of the study (unless defined by local practice protocols)<br>Medications disallowed included: other investigational drugs; anti-tumour therapies including chemotherapy, hormone therapy, radiation therapy, gene therapy, biologics, or immunotherapy, any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert | Medications included: any medication considered necessary for patient's welfare not expected to interfere with evaluation of study<br>Primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement of the study (unless defined by local practice protocols)<br>Medications disallowed included: other investigational drugs; anti-tumour therapies including chemotherapy, hormone therapy, radiation therapy, gene therapy, biologics, or immunotherapy, any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert |
| Primary outcomes | Overall survival | Overall survival and progression-free survival |
| Secondary outcomes | Progression-free survival, objective response rate and safety | Objective response rate, safety and health-related quality of life |

ECOG=Eastern Cooperative Oncology Group; G-CSF=granulocyte-colony stimulating factor; HER2=human epidermal growth factor receptor 2; HRQoL=health-related quality of life; IV=intravenous; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; PS=performance status; TPC=Treatment of Physician's Choice
Source: CS, adapted from Table 12

## 4.4 Statistical approach adopted for the conduct and analysis of studies included in the systematic review

The ERG has extracted information relevant to the statistical approach adopted for the conduct of, and analysis of data from, the EMBRACE trial from the CSR,[23] updated CSR,[22] the trial statistical analysis plan (TSAP),[31] the trial protocol [32] and the CS. Since Study 301 was only used to derive HRQoL data, the ERG has not critiqued the statistical approach adopted for the conduct of this trial; ERG comment on HRQoL data is provided in Section 4.8.6.

### 4.4.1 Outcomes analysed

The definitions and measures used to assess the primary and secondary efficacy outcomes from the EMBRACE trial are listed in Table 7.

Table 7 Primary and secondary efficacy outcomes of the EMBRACE trial

| Outcome | Definition | Assessment Measures |
|---|---|---|
| OS | Defined as the time from the date of randomisation until death from any cause | • Survival was recorded during the study and following treatment discontinuation for any reasons other than consent withdrawal. Follow-up for survival was assessed at three-monthly intervals until death |
| PFS | Defined as the time from randomisation until disease progression or death due to any cause in the absence of disease progression | • Tumour assessment was performed according to the RECIST methodology. Baseline tumour assessments were performed within 4 weeks of the start of treatment, consisting of: CT or MRI scans of the chest, abdomen, pelvis, and any other areas of suspected disease; photographs of skin lesions (if present); and bone scans<br>• Tumour assessments were performed in all patients at eight-weekly intervals (± 1 week), or sooner if there was suspicion of disease progression. Scans and photography were performed in those areas where disease was found at baseline, and in any new areas of suspected disease. Bone scans were only repeated during the study if clinically indicated. Tumour responses were confirmed by a second assessment ≥ 4 weeks later. Patients with CR/PaR or SD, who withdrew from treatment before disease progression, continued to have tumour assessments every 3 months until progressive disease or the start of a new anticancer treatment<br>• Tumour assessments were made by investigators via imaging data and clinical examinations. Imaging data was independently reviewed in a blinded fashion at a central facility<br>• Analyses were conducted based on both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data |
| ORR | Defined as the number of patients with a confirmed CR or confirmed PaR divided by the number of patients in the analysis population | • Analyses were conducted based on both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data<br>• Tumour response was evaluated according to RECIST criteria<br>• Target and non-target lesions were assigned to response assessment categories, and the overall tumour response determined for all possible combinations of target and non-target lesions, with or without the occurrence of new lesions |

CR=complete response; CT=computed tomography; MRI=magnetic resonance imaging; OS=overall survival; ORR=objective response rate; PaR=partial response; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumours; SD=stable disease
Source: CS, adapted from Table 9

Safety data from the EMBRACE trial were presented as summaries of all AEs, serious AEs (SAEs), deaths, treatment-related AEs and treatment discontinuation due to AEs. HRQoL data were not collected during the EMBRACE trial.

### 4.4.2 ERG critique of statistical approach

The statistical methods employed by the company to analyse the outcome data from the EMBRACE trial are summarised in the Appendices to this ERG report (Section 11.2). The ERG notes that, the company has analysed outcome data from three data-cuts:

- the primary analysis was planned to occur when 411 deaths had been recorded, although the data cut-off point for the primary analysis was actually after 422 (55%) patients had died (12 May 2009)
- an updated analysis of OS was conducted at the request of the regulatory authorities, when 77% of deaths had occurred, representing a more mature dataset with longer follow up (3 March 2010 data cut-off point)
- the most recent OS analysis was performed after 95% of patients had died, and the company presented data for Subgroup 2 patients using this most recent data cut-off (17 June 2013).

During the clarification process the ERG requested results for the ITT population using the data available after 95% of patients had died. The ERG considered that this information was required to allow a comparison of outcomes for the Subgroup 2 and ITT populations. Results for the ITT and Subgroup 2 populations that have been generated using data from the most recent data cut are provided in Section 4.8 of this ERG report.

The analyses carried out by the company to generate OS and PFS hazard ratios (HRs) were conducted using Cox proportional hazards (PH) modelling. The validity of this method relies on the hazards of the two comparator drugs being proportional.

As part of the clarification process, the ERG requested details of any PH testing that had been carried out by the company. The company response explained that no formal testing of the PH assumption had been performed. To test the validity of the PH assumptions required to generate valid HRs the ERG plotted the OS cumulative hazards for patients treated with eribulin against those for patients treated with TPC. The same approach was taken in relation to PFS data. Data sources for, and results from, these analyses are summarised in Table 8

Table 8 Results from the ERG's proportional hazard tests

| Outcome | Data source | PH assumption valid? |
|---|---|---|
| **ITT population** | | |
| OS | Cumulative hazards estimated from digitised K-M data presented in the CS Figure 9 (OS) and Figure 11 (PFS) | Yes |
| PFS | | No – validity of company HR unclear and HRs may not be reliable |
| **Subgroup 2 population** | | |
| OS | K-M data provided during the clarification process (in response to ERG question B1) used to calculate cumulative hazards. | No – validity of company HR unclear and HRs may not be reliable |
| PFS | | No – validity of company HR unclear and HRs may not be reliable |

ERG=Evidence Review Group; HR=hazard ratio; K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival

A summary of the checks made by the ERG in relation to the statistical approach adopted by the company to analyse data from the EMBRACE trial is provided in Table 9. With the exception of the lack of PH testing, overall, having carried out these checks, the ERG is satisfied with the statistical approach employed by the company. The ERG therefore has confidence in the validity of the results from the trial, with the exception of the interpretation of HRs where the assumption for PH does not hold.

Table 9 ERG assessment of statistical approach used to analyse data from the EMBRACE trial

| Component of statistical approach | Approach taken with ERG comment |
|---|---|
| Sample size calculation | The ERG was able to replicate the sample size calculation provided in the CS (p64) using the sample size details provided by the company for the original sample size calculation. However, the ERG notes that the company have performed a sample size re-estimation but do not provide further details in order to calculate the sample size re-estimation. The ERG is unable to comment on the sample size calculation as it is unclear whether the sample size re-estimation has affected the power or type 2 error in any way. |
| Protocol amendments | The ERG notes that four amendments were made to the original EMBRACE trial protocol. These are outlined and provided in the final analysis CSR (Section 8.9). These do not appear to be a cause for concern. However, the ERG also notes that the company made some changes to the planned analyses after database lock including:<br>• To further investigate TPC the agents were grouped into seven groups based on the IVRS data, as capecitabine, vinorelbine, gemcitabine, taxanes, anthracyclines, other chemotherapy and hormonals, and some tables were repeated using these groups. Comparisons between the eribulin and TPC arm were conducted in two ways for some analyses: 1) eribulin patients who would have received that TPC if they had been randomized to that group against those that did, and 2) all patients who received eribulin versus the individual TPC group.<br>• The parameters HER2, prior capecitabine and geographical region were fitted using the strata statement in the Cox model, rather than as covariates. The inclusion of stratification variables as strata rather than covariates in the Cox model produces a hazard ratio which reflects the results from the primary analysis conducted using the stratified log-rank test more appropriately.<br>• In addition to the PFS analyses as detailed in the SAP, following unblinding, discussion surrounding the interpretation of the "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" led to the formulation of a new set of PFS rules for censoring/progression. As such, this approach represents a post hoc analysis, as the methods used to define and interpret the results were not part of the pre-specified analysis. This analysis is based upon the Independent review of the radiological assessments. For details of this analysis please see the SAP. The main difference from this analysis as opposed to the PFS detailed in the SAP is that it takes into account progressions from non-target lesions (i.e. unequivocal progressions) in addition to new lesion and target lesion progression events.<br>However, the company do not present the results for these post-hoc analyses or critique them in the CS, therefore the ERG is satisfied that these post-hoc analyses are not a cause for concern |
| Sensitivity analyses for OS | The ERG is satisfied that the results of the sensitivity analysis (primary OS analysis adjusted for number of prior chemotherapy regimens and ER status) is provided in the CSR |
| Subgroup analyses for OS | A total of 17 subgroup analyses were pre-specified in the CSR. The ERG is satisfied that the results of all pre-specified subgroup analyses are provided in the CSR and notes one of these includes Subgroup 2 on which the company focusses the CS. The ERG also notes that some post-hoc subgroup analysis results are also provided in the CSR which should be interpreted with caution |
| Adverse events | Safety was assessed through summaries of all AEs, SAEs, deaths, treatment-related AEs and discontinuation due to AEs. The ERG is satisfied that the results of all the AE data analyses are provided in both the primary analysis and final analysis CSRs |

AE=adverse event; CSR=clinical study report; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer quality of life questionnaire with breast module; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire 30; ER=oestrogen receptor; HER2=human epidermal growth factor receptor 2; IVRS=interactive voice recognition system; OS=overall survival; PFS=progression-free survival; SAE=serious adverse event; SAP=statistical analysis plan; TPC=Treatment of Physician's Choice
Source: CS, CSR, updated CSR and ERG comment

## 4.5 Patient populations relevant to the current appraisal

As noted in Section 1.1, the company presents evidence for all patients receiving ≥3 chemotherapy regimens for LABC/MBC (the ITT population) and for a subgroup of this population, Subgroup 2. As noted in Sections 4.2 and 4.3, HRQoL data from Study 301 have been provided. The different populations are summarised in Table 10.

Table 10 Summary of populations referred to in the evidence for clinical effectiveness

| Trial/ population | Description | Relevant population in decision problem | Relevant outcomes |
|---|---|---|---|
| EMBRACE trial ITT population | All patients who had received at least two prior chemotherapy regimens for LABC/MBC who were randomised, irrespective of whether or not they actually received study treatment or whether they received the medication they were randomised to | All patients receiving ≥3 chemotherapy regimens for LABC/MBC<br><br>(Original indication for eribulin) | OS<br>PFS<br>ORR |
| EMBRACE trial safety population | All patients who had received at least two prior chemotherapy regimens for LABC/MBC who were randomised and who received at least a partial dose of study treatment. The population was based on the actual treatment received | All patients receiving ≥3 chemotherapy regimens for LABC/MBC<br><br>(Original indication for eribulin) | AEs |
| EMBRACE trial Subgroup 2 population | Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated)<br>This comprises 73.4% of the EMBRACE ITT population and 73.3% of the EMBRACE safety population | Subgroup 2: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated) | Subgroup of ITT population:<br>• OS<br>• PFS<br>• ORR<br><br>Subgroup of safety population:<br>• AEs |
| Study 301 third-line patients | Patients with LABC/MBC whose disease has progressed after two prior chemotherapy regimens for advanced disease which excludes capecitabine | A subgroup of the ITT population | HRQoL |

AEs=adverse events; HRQoL=health related quality o of life; ITT=intention-to-treat; LABC/MBC=locally advanced breast cancer/metastatic breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

## *4.6 Patient characteristics of the studies included in the systematic review*

### 4.6.1 Patient disposition

All patients in the EMBRACE trial at the time of the most recent data-cut (after 95% of patients had died). At the time of the primary analysis, when 55% of patients had died, 33 (4.3%) patients were still on study treatment.

Reasons for discontinuing treatment were provided by the company for the ITT population after 55% of patients had died and for Subgroup 2 patients after 95% of patients had died. Despite the analyses being carried out at different time points the reasons appear similar in both populations (see Table 11). The most common reason for discontinuing treatment was disease progression.

Table 11 Patient disposition* in the EMBRACE trial – safety population and Subgroup 2*

| Reason for treatment discontinuation | Overall trial population | | | | Subgroup 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Eribulin (N=508) | | TPC (N=254) | | Eribulin (n=370) | | TPC (n=189) | |
| Patients randomised (ITT population) | 508 | | 254 | | 370 | | 189 | |
| Patients who withdrew prior to receiving any treatment | -6 | | -6 | | -4 | | -5 | |
| Patients who were treated on the opposite treatment arm | +1 | | -1 | | +1 | | -1 | |
| Patient who received at least some study treatment (Safety population) | 503 | (100.0) | 247 | (100.0) | 367 | (100.0) | 183 | (100.0) |
| Progressive disease, n (%) | 335 | (66.6) | 152 | (61.5) | 263 | (71.7) | 118 | (64.5) |
| Clinical progression, n (%) | 60 | (11.9) | 36 | (14.6) | 46 | (12.5) | 23 | (12.6) |
| Adverse event, n (%) | 49 | (9.7) | 24 | (9.7) | 34 | (9.3) | 21 | (11.5) |
| Physician decision, n (%) | 18 | (3.6) | 11 | (4.5) | 14 | (3.8) | 9 | (4.9) |
| Withdrawal by subject, n (%) | 9 | (1.8) | 5 | (2.0) | 5 | (1.4) | 5 | (2.7) |
| Death, n (%) | 3 | (0.6) | 2 | (0.8) | 2 | (0.5) | 2 | (1.1) |
| Other, n (%) | 5 | (1.0) | 8 | (3.2) | 3 | (0.8) | 5 | (2.7) |
| On treatment, n (%) | 24 | (4.8) | 9 | (3.6) | 0 | (0.0) | 0 | (0.0) |

*Patient disposition reported in the CS for the ITT population (when 55% of patients had died) and, for the Subgroup 2 population when 95% of patients had died

Source: CS, adapted from Figure 7 and company response to ERG clarification letter (question A1)

### 4.6.2 Baseline characteristics

Of the 762 patients recruited to the EMBRACE trial, 51 were from UK centres. The ERG is satisfied that a sufficient number of patients in the trial were from European Union countries that implement care pathways similar to those found in the UK, meaning that findings from the EMBRACE trial can be considered generalisable to NHS clinical practice.

Demographic data, baseline disease, and tumour characteristics are provided in the CS for each treatment arm of the EMBRACE trial for the ITT population and the Subgroup 2 population. These data are reproduced in the Appendices to this ERG report (Section 11.1, Table 39). The ERG considers that the presented data suggest that patient characteristics are well balanced across treatment groups. In summary:

- the majority of patients were Caucasian (>90%)
- the median age of patients was 55 years
- approximately three quarters of women were post-menopausal
- the majority of patients had ER-positive (≥70%) and/or HER2-negative (≥82%) LABC/MBC
- the majority of patients had ECOG PS 0 (≥42%) or ECOG PS 1 (≥48%)
- the most common sites for metastases were bone (>60%) and liver (>60%)
- the median time since diagnosis was just over 5 years.

The ERG notes that in the CS (Appendix 3), the company observes that disease stage at diagnosis differs by trial arm. Information in the CSR, suggests that the main difference between arms is that, at diagnosis, [redacted] of patients treated with eribulin had Stage II disease and [redacted] had Stage IV disease. In contrast, at diagnosis, [redacted] of patients treated with TPC had Stage II disease and [redacted] had Stage IV disease.

The majority of patients (59.4%) in the EMBRACE trial were treated with one of the chemotherapy regimens specified in the final scope issued by NICE and company's decision problem, i.e. vinorelbine, capecitabine or gemcitabine. As noted in Section 2.6 of this ERG report, NICE recommends both capecitabine and vinorelbine as second- or third-line treatments (CG81).[8] Gemcitabine is also a NICE recommended treatment but only in combination with paclitaxel (TA116).[33] It is, however, apparent from Table 12 that only one patient who received gemcitabine also received paclitaxel. Clinical advice to the ERG is that the use of gemcitabine monotherapy is not uncommon for more heavily pre-treated patients. The ERG considers that the TPC agents supplied to EMBRACE trial participants mostly reflect those that are prescribed in NHS clinical practice.

Importantly, 73% of patients in the EMBRACE trial had previously received treatment with capecitabine. These patients were those that constitute Subgroup 2. The characteristics of the Subgroup 2 population are broadly similar to those of the ITT population. The main exceptions are:

- approximately 64% of Subgroup 2 patients had received four or more prior chemotherapy regimens (in any setting) compared with approximately 53% of all patients in the ITT population
- approximately 65% of Subgroup 2 patients had received three or more prior chemotherapy regimens in the LABC/MBC setting compared with approximately 57% of all patients in the ITT population.

The ERG considers that the line of treatment differences are not unexpected since patients in Subgroup 2 had also received prior capecitabine in addition to an anthracycline and taxane. In addition, as approximately 70% of Subgroup 2 patients were from region 1 (North America, Western Europe and Australia) compared with approximately 64% in ITT population, the ERG considers that differences in capecitabine use across the countries in each region may account for these marginal differences between the ITT and Subgroup 2 populations.

Table 12 EMBRACE trial Treatment of Physician's Choice (ITT and Subgroup 2 populations)

| TPC agent | ITT population | | Subgroup 2 | |
|---|---|---|---|---|
| | N | % | n | % |
| Chemotherapy | 238 | 93.7 | 174 | 92.1 |
| • Vinorelbine | 61 | 24.0 | 54 | 28.6 |
| • Gemcitabine* | 46 | 18.1 | 38 | 20.1 |
| • Capecitabine | 44 | 17.3 | 4§ | 2.1§ |
| • Taxanes | 38 | 15.0 | 37 | 19.6 |
| ○ Paclitaxel† | 25 | 9.8 | 25 | 13.2 |
| ○ Docetaxel | 10 | 3.9 | 9 | 4.8 |
| ○ Ixabepilone | 3 | 1.2 | 3 | 1.6 |
| • Anthracyclines | 24 | 9.5 | 22 | 11.6 |
| ○ Doxorubicin‡ | 23 | 9.1 | 21 | 11.1 |
| ○ Mitoxantrone | 1 | 0.4 | 1 | 0.5 |
| • Other chemotherapy | 25 | 9.8 | 19 | 10.1 |
| Hormonal therapy | 9 | 3.6 | 9 | 4.8 |
| Other¥ | 7 | 2.8 | 6 | 3.2 |
| TOTAL* | 254 | 100.0 | 189 | 100.0 |

ITT=intention-to-treat; TPC=Treatment of Physician's Choice.
* One patient (included in both the ITT population and Subgroup 2) received gemcitabine and paclitaxel and is included in the gemcitabine group only
§ Four patients in the TPC arm received capecitabine in the EMBRACE trial even though they had been previously treated with capecitabine prior to entry into the trial
† Paclitaxel includes paclitaxel and nab-paclitaxel
‡ Doxorubicin includes doxorubicin and liposomal doxorubicin

¥ Patients were discontinued prior to treatment initiation or received eribulin instead of the planned TPC
Source: CS, adapted from Table 15 and company response to further ERG clarification

The company states that patients could have been treated with trastuzumab in centres where trastuzumab was available. However, at the time of the EMBRACE trial, trastuzumab was not commonly used and so was not actually employed as part of TPC. The ERG does not consider this to be a limitation of the EMBRACE trial since trastuzumab is only an option for patients with HER2-positive disease (17.8% of ITT population) and, for these patients, trastuzumab would be a treatment option much earlier in the treatment pathway.

## 4.7 Quality assessment of the RCTs included in the systematic review

The CS includes an assessment of the risk of bias for the EMBRACE trial. This is reproduced in Table 13. The company has also provided an assessment of the risk of bias for Study 301. As data from Study 301 were used to provide information about HRQoL for the current STA, the ERG has also reproduced this assessment in Table 13. Additional information is provided in the appendices to this ERG report (Section 11.4). Overall, the ERG considers that both the EMBRACE trial and Study 301 were generally well designed and well conducted and the ERG agrees with the company's conclusion that both trials have at a low risk of bias.

Table 13 Company's assessment of risk of bias for the EMBRACE trial and Study 301

| Study question | Company assessment | | ERG Comment |
|---|---|---|---|
| | EMBRACE | Study 301 | |
| Was randomisation carried out appropriately? | Yes | Yes | Agree |
| Was the concealment of treatment allocation adequate? | NA | NA | As randomisation was conducted centrally, using an IVRS in both trials ensured that a patient's allocation to a particular treatment arm could not be predicted or influenced. In the EMBRACE trial, the use of an IVRS also ensured that each TPC treatment was independently randomised against eribulin to support the conduct and results of subgroup analyses |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes | Yes | Agree |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | NA | NA | The primary outcome of the EMBRACE trial (OS) was not dependent on subjective assessment. All other relevant efficacy outcomes in EMBRACE were dependent on subjective assessment (PFS and ORR) but blinded review was also conducted in addition to investigator assessment for these outcomes, enabling a comparison to be made to assess risk of bias. Safety data in EMBRACE were also reviewed by the independent DMC. HRQoL data were not blinded in Study 301 |
| Were there any unexpected imbalances in drop-outs between groups? | No | No | Agree |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No | No | Agree, all outcomes were reported in the relevant CSRs. Note, for this STA, OS, PFS, ORR and safety are relevant outcomes from EMBRACE and HRQoL is the only relevant outcome from Study 301 |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes | Yes | Agree |

CSR=clinical study report; DMC=data monitoring committee; HRQoL=health-related quality of life; NA=not applicable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; STA=single technology appraisal; TPC=Treatment of Physician's Choice; IVRS=interactive voice response system
Source: CS, adapted from Table 22 and Appendix 3

## *4.8 Results from the studies included in the systematic review*

OS analyses of EMBRACE trial data were conducted at three points in time: primary analysis after 55% of patients had died, updated analysis after 77% of patients had died and the most recent analysis, after 95% of patients had died. PFS analyses were conducted at the primary analysis (after 55% of patients had died) and most recent analysis (after 95% of patients had died). The company also provides ORR results and safety data from the primary analysis. As HRQoL data were not collected as part of the EMBRACE trial, the company has presented data for this outcome from Study 301.

The company only presents OS and PFS results for Subgroup 2 patients. These were calculated using data from the most recent data-cut, i.e. after 95% of patients had died. As a result of a clarification request (question A9), the company also provided some safety data for Subgroup 2 patients.

### 4.8.1 Overall survival

The ERG cautions that the company's OS HR (but not median OS) result calculated from Subgroup 2 population data may be unreliable. This is because the approach taken to calculate relies on the assumption that the OS K-M data from the intervention and comparator arms of a trial are proportional to one another. Analyses undertaken by the ERG indicate that while the ITT population OS K-M data are proportional the Subgroup 2 OS K-M data are not proportional (see Table 14).

The ITT and Subgroup 2 OS results generated using the latest data-cut (i.e. after 95% of patients had died) were very similar, with median OS for patients treated with eribulin being ≥13 months (Table 14). Improvements versus TPC of between 2.7 and 2.9 months were observed in the ITT population and Subgroup 2 patients, respectively. This improvement was found to be statistically significant for both the ITT population and the Subgroup 2 population; however, as the log rank test also relies on the assumption of proportional hazards, the results of this test should be interpreted with caution when considering the OS data from Subgroup 2 patients.

Table 14 EMBRACE trial overall survival after 95% of patients had died (ITT population and Subgroup 2 populations)

| Parameter | ITT population | | Subgroup 2 | |
|---|---|---|---|---|
| | Eribulin (N=508) | TPC (N=254) | Eribulin (n=370) | TPC (n=189) |
| Number of patients who died, n (%) | 485 (95.5) | 242 (95.3) | 356 (96.2) | 183 (96.8) |
| OS, months | | | | |
| Median (95% CI) | 13.24 (12.06 to 14.4) | 10.55 (9.23 to 12) | 13.0 (11.7 to 13.8) | 10.1 (7.7 to 11.4) |
| Difference in medians (95% CI) | 2.7 (1 to 4.4) | | 2.9 (NA) | |
| Stratified log-rank test | p=0.011 | | p=0.008 | |
| Hazard ratio (95% CI) | 0.815 (0.696 to 0.955) | | 0.78 (0.65 to 0.94) | |

CI=confidence interval; NA=not available; TPC=treatment of physician choice
Source: Company response to ERG clarification letter, adapted from Table A1

The median OS results for the ITT population which were calculated from the latest data-cut are similar to the median OS reported at both the previous data-cuts, at which points statistically significant improvement in the eribulin arm were also reported (median OS, eribulin versus TPC, primary analysis: 13.1 versus 10.6 months, p=0.041; updated analysis: 13.2 versus 10.6 months, p=0.014). The company's updated analysis demonstrates that the survival curves separate early and remain separated for the duration of the analysis period.

Any treatment given to patients following disease progression has the potential to impact on OS and, as part of the clarification process, the ERG requested details of any post-progression treatments given to patients in both arms of the EMBRACE trial. Details relating to these treatments are summarised in (Table 15). Overall, more patients in the eribulin arm appear to have received more treatment on progression. In particular, it is noticeable that the five most common treatments prescribed post-progression are the five most common agents administered in the TPC arm of the EMBRACE trial. During the previous appraisal of eribulin (TA250), the ERG noted (p24):

> *"The post-progression treatments given appear to be similar in number and type across both arms of the trial thereby minimising the likelihood of affecting the OS results."*[34]

This conclusion was based on data provided by the company for a previous data-cut. Since then, the proportion of patients receiving additional treatment has increased to a greater extent in the eribulin arm than in the TPC arm. However, given that the OS results remain similar, it appears that rather than the additional treatments being an important contributory factor to OS, they simply reflect the fact that patients in the eribulin arm are living longer and so have more time to receive additional treatments.

Table 15 Subsequent treatment received on disease progression (EMBRACE trial ITT and Subgroup 2 populations)

| Treatment on disease progression | ITT population | | Subgroup 2 | |
|---|---|---|---|---|
| | Eribulin (N=508) | TPC (N=254) | Eribulin (n=370) | TPC (n=189) |
| Any, n (%) | 394 (77.6) | 164 (64.6) | 290 (78.4) | 123 (56.1) |
| Most common* treatments | | | | |
| • Capecitabine | 58 (11.4) | 6 (2.4) | 8 (2.2) | 0 (0.0) |
| • Vinorelbine | 49 (9.7) | 17 (6.7) | 41 (11.1) | 9 (4.8) |
| • Gemcitabine | 34 (6.7) | 24 (9.5) | 29 (7.9) | 17 (9.0) |
| • Paclitaxel | 42 (8.3) | 15 (5.9) | 39 (10.5) | 12 (6.4) |
| • Doxorubicin | 40 (7.9) | 7 (2.8) | 31 (8.4) | 4 (2.1) |
| • Cyclophosphamide | 22 (4.3) | 10 (3.9) | 21 (5.7) | 9 (4.8) |

* >5% in any arm
Source: Company response to ERG clarification letter, adapted from response to A8

### 4.8.2 Progression-free survival

Analyses carried out using EMBRACE trial data from the latest data cut (after 95% of patients had died) show that ITT and Subgroup 2 population results for median PFS are very similar (Table 16), with PFS for patients treated with eribulin being approximately 3.6 months and improvements versus TPC of between 1.4 and 1.5 months (ITT and Subgroup 2 populations respectively). These results are similar to the primary analysis median PFS results for both trial arms.

Table 16 EMBRACE trial progression-free survival (investigator assessment) using the latest data cut (after 95% of patients had died), ITT and Subgroup 2 populations

| Parameter | ITT population | | Subgroup 2 | |
|---|---|---|---|---|
| | Eribulin (N=508) | TPC (N=254) | Eribulin (n=370) | TPC (n=189) |
| Number of patients who progressed or died to n (%) | 453 (89.2) | 217 (85.4) | 334 (90.2) | 161 (85.1) |
| PFS to months | | | | |
| Median (95% CI) | 3.61 (3.29 to 3.75) | 2.17 (1.97 to 2.76) | 3.6 (3.3 to 3.8) | 2.1 (1.9 to 2.2) |
| Difference in medians (95% CI) | 1.4 (NA) | | 1.5 (NA) | |
| Stratified log-rank test | p=0.002 | | p<0.001 | |
| Hazard ratio (95% CI) | 0.771 (0.651 to 0.913) | | 0.68 (0.56 to 0.83) | |

CI=confidence interval; NA=not available; PFS=progression-free survival; TPC=treatment of physician choice
Source: Company response to ERG clarification letter, adapted from Table A1

At the time of the primary analysis, the company also reported PFS by independent review for the ITT population. At that time median PFS was similar in both the eribulin and TPC arms of the trial irrespective of whether assessed by the investigator (3.6 months for patients treated with eribulin versus 2.2 months for patients treated with TPCy) or by independent review (3.7 months for patients treated with eribulin versus 2.2 months for patients treated with TPC). The ERG considers that the similarity of the investigator and independent assessed PFS from the primary analysis, and the similarity of the findings to the investigator assessed PFS reported at the most recent data cut (after 95% of patients had died [3.61 versus 2.17 months]) suggests the PFS findings are robust and reliable for the overall population.

Overall, the ERG considers that the findings from the EMBRACE trial demonstrate an improvement in PFS for patients treated with eribulin versus those treated with TPC. This is true for the ITT population and for the Subgroup 2 population. However, the ERG cautions that the company's ITT and Subgroup 2 PFS hazard ratio (but not median PFS) results may be unreliable as the approach taken to calculate these values is only valid if the relevant PFS K-M data are proportional to one another and analyses carried out by the ERG indicate that, for both patient populations, the data are not proportional (see Table 8).

### 4.8.3 Objective response rate

The company has only reported the primary analysis ORR for the ITT population. The ORR was statistically significantly different in favour of eribulin compared with TPC for both independent-based (12.2% [95% CI 9.4 to 15.5] versus 4.7% [95%CI 2.3 to 8.4] p=0.002) and investigator-based assessments (13.2% [95% CI 10.3 to 16.7] versus 7.5% [95% CI 4.3 to 11.9] p=0.028). The ERG agrees with the company that the magnitude of the ORR should be considered in the context of the population enrolled in the EMBRACE trial as all patients had received at least two previous chemotherapies for LABC/MBC.

### 4.8.4 Safety

EMBRACE trial primary analysis (after 55% of patients had died) AEs are reported in the CS. Information about AEs experienced by Subgroup 2 patients is not reported in the CS. However, during the clarification process, the company confirmed that the AE data available for Subgroup 2 patients indicate that there are no notable differences between the AE experience of the overall safety population and that of the Subgroup 2 population (response to ERG clarification letter, A9). The company supported this statement by providing data on the most commonly reported AEs for Subgroup 2 patients in each arm of the EMBRACE trial (>10% in either arm). Based on the provided data, the ERG agrees with the company that, in terms of AE experience, there are no notable differences between the EMBRACE trial safety population and the Subgroup 2 population.

A comparison of safety between treatment with eribulin and treatment with TPC is subject to the following caveats:

- as a group, patients in the TPC arm received a wide range of treatments, each of which has a distinct safety profile
- the number of patients receiving each type of TPC was relatively small
- in the EMBRACE trial, overall exposure to study treatment was longer in the eribulin arm compared in the TPC arm (median 3.9 months versus 2.1 months [chemotherapy] and 1 month [hormonal], respectively)

These factors mean that reliable conclusions cannot easily be drawn when comparing incidences of specific AEs in the two arms of the trial.

The overall incidence of AEs experienced by patients participating in the EMBRACE trial is presented in Table 33 of the CS. This table includes details about any AEs, SAEs (including fatal SAEs) and severe AEs. Key points include:

- **Any AE**: most patients experienced at least one AE (98.8% of patients in the eribulin arm and 93.1% in the TPC arm)
- **Severe AEs** (Grade ≥3): these occurred more frequently in the eribulin arm than in the TPC arm (90.7% versus 59.5%). The company (CS, p120) notes that the most common Grade ≥3 AE for patients treated with eribulin was neutropenia (49.7%); however, the most common Grade ≥3 AEs for patients treated with TPC agents are not reported
- **Any SAE**: the incidence of SAEs was similar in both arms of the trial (eribulin: 25.0%, TPC: 25.9%). The company (CS, p113) notes that the most frequently reported SAEs in the eribulin arm were febrile neutropenia (4.2%) and neutropenia (1.8%); the most frequently reported events in the TPC arm were dyspnoea (3.6%) and asthenia (2.4%)
- **Fatal SAEs**: There were fewer fatal AEs in the eribulin arm (4.0%) than in the TPC arm (7.3%). Fatal AEs were more noticeable with capecitabine (9.1%) and gemcitabine (8.7%) compared with eribulin (4.0%).

**Most commonly reported adverse events**

Details relating to the most frequently reported all-Grade AEs (>10% patients in each arm) in the EMBRACE trial are provided in Table 34 of the CS. The most frequently reported AEs occurring in patients treated with eribulin are reported to be asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), peripheral neuropathy (34.6%) and nausea (34.6%). From Table 34 of the CS it is, however, evident that similar incidences of asthenia/fatigue (50.8%) and neutropenia (49.2%) were seen in patients treated with vinorelbine. For patients treated with TPC the most common AEs were asthenia/fatigue (39.7%), neutropenia (29.6%), nausea (28.3%), anaemia (22.7%) and constipation (20.6%). Only the incidences of anaemia and constipation are higher in the TPC arm than in the eribulin arm (18.7% and 24.7% respectively in patients treated with eribulin).

**Treatment related adverse events**

In total, 94.2% of patients reported AEs that were considered by the investigator to be treatment-related in the eribulin arm compared with 77.7% in the TPC arm (CS, Table 33). The company notes (CS, p113) that the open-label nature of the trial means that these figures may be subject to bias against the investigational agent (eribulin).

**Adverse events leading to treatment discontinuation**

The company states that discontinuations due to AEs were lower in the eribulin arm (13.3%) than in the TPC arm (15.4%). However, the ERG observes that discontinuations due to AEs were all marginally lower for patients treated with vinorelbine (11.5%), capecitabine (10.9%) and gemcitabine (10.9%) than for patients treated with eribulin, suggesting that the apparently higher treatment discontinuation rate in the TPC arm can be attributed to the other agents that constituted TPC. Indeed, information in the CSR (Table 23) shows that this was a particular issue for patients treated with taxanes [redacted].

**Real world evidence**

The company reports (CS, p118) that recently published data from audits undertaken in England, Spain and France/Switzerland have shown that eribulin is well tolerated in a routine clinical practice setting and reflect that patients are not impacted greatly by the side effect profile of eribulin (see Section 4.9). The company concludes that eribulin has a well characterised and manageable safety profile.

### 4.8.5 Exposure to study drugs

In the EMBRACE trial, overall exposure to study treatment was longer in the eribulin arm than in the TPC arm. This was observed for all patients in the EMBRACE trial (safety population) and Subgroup 2 patients (Table 17). The median number of cycles of eribulin received by patients was reported in the CS to be between five and six. It is reported in the CS that patients in the eribulin arm received the study drug for almost twice as long as those in the TPC arm. The company considers that the longer duration of therapy demonstrates the superior efficacy and tolerability of eribulin compared with TPC, since therapy was discontinued on disease progression and PFS was longer for patients in the eribulin arm than it was for those receiving TPC. The company further states that evidence from the EMBRACE trial highlights the positive safety and tolerability profile associated with treatment with eribulin.

Table 17 EMBRACE trial exposure to study drugs (safety and Subgroup 2 populations, 95% data-cut)

| Parameter | Overall safety population | | | Subgroup 2 | |
|---|---|---|---|---|---|
| | Eribulin (N=503) | TPC (Chemotherapy) (N=238) | TPC (Hormonal) (N=9) | Eribulin (n=367) | TPC (n=183) |
| Duration of exposure, median days (min, max) | 118 (21, 1241) | 70.0 (1, 1578) | 30.0 (25, 188) | 119 (21, 1241) | 55 (1, 1578) |
| Number of cycles completed on study, n (%) | | | | | |
| 1 to 2 | 81 (16.1%) | NA | NA | 57 (15.5%) | NA |
| 3 to 4 | 127 (25.2%) | | | 91 (24.8%) | |
| 5 to 6 | 110 (21.9%) | | | 86 (23.4%) | |
| > 6 | 185 (36.8%) | | | 133 (36.2%) | |
| Range | 1 to 55 cycles | | | 1 to 55 cycles | |
| Dose intensity, median mg/m$^2$/week (min, max) | 0.84 (0.2, 1.0) | NA | NA | 0.84 (0.2, 1.0) | NA |
| Relative dose intensity, % (min, max) | 91% (30, 110) | NA | NA | 90% (30, 110) | NA |
| Patients with dose interruption, n (%) | 29 (5.8%) | 22 (9.2%) | 2 (22.2%) | 26 (7.1 %) | 14 (7.7%) |
| Patients with dose delay, n (%) | 253 (50.3%) | 100 (42.0%) | 0 (0.0%) | 188 (51.2%) | 75 (41.0%) |
| Patients with dose reduction, n (%) | 146 (29.0%) | 63 (26.5%) | 0 (0.0%) | 109 (29.7%) | 46 (25.1%) |

NA=not applicable; TPC=treatment of physician choice
Source: Company response to ERG clarification letter, A4

### 4.8.6 Health-related quality of life

HRQoL data were not collected as part of the EMBRACE trial but were collected during Study 301. In Study 301 change in HRQoL was a secondary endpoint. The ERG notes that no patient in Study 301 had received more than two lines of treatment and no patient had received prior capecitabine. The ERG cautions, therefore, that the HRQoL findings presented in the CS may only be representative of a fitter subgroup of the EMBRACE trial ITT population and may not be representative of the experience of Subgroup 2 patients.

HRQoL data were collected using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QoL) questionnaire[35] and the breast module QLQ-BR23.[36] The EORTC-C30 questionnaire is a validated instrument commonly used in oncology trials.

Data were collected at baseline in clinic before randomisation and then at 6 weeks and 3, 6, 12, 18 and 24 months (or disease progression/treatment change) and at unscheduled visits. Questionnaires were completed prior to any study-related procedures for that visit and before tumour assessment results were communicated to the patient. Patients were asked to complete questionnaires at each clinic visit, even if they had declined previously. Compliance for completing the EORTC QLQ-C30 questionnaires during the study was ≥85% until 12 months, but thereafter sample sizes decreased due to study attrition. The company cautions that, due to the smaller sample sizes, analyses after 6 months should be interpreted with caution.

The principal pre-specified HRQoL outcome in Study 301 was overall global health status (GHS)/quality of life (QoL) at week 6. However, the results reported in the CS are based on additional post-hoc analyses of the study data.

Only data from a subgroup of patients in Study 301 were relevant to all patients receiving ≥3 chemotherapy regimens for LABC/MBC, namely a proportion (28%) of those who had received third-line treatment (n=309). No patient had previously received capecitabine.

The only results reported in the CS for all patients receiving ≥3 chemotherapy regimens for LABC/MBC are scores for GHS. The ERG highlights that HRQoL appears to improve over time (CS, Figure 18 with scores reproduced in Table 18). The baseline GHS score is identical for patients receiving eribulin as a third-line treatment and for patients receiving capecitabine as a third-line treatment (55.2). The score for patients in the eribulin arm rose to 83.3 at 24 months and for patients receiving capecitabine it rose to 68.1, indicating that improvement was greatest in patients treated with eribulin. However, as mentioned previously, the data must be treated with caution due to the low number of patients completing the questionnaire at 24 months (primarily due to most patients having progressed

or having changed treatment by this stage; only 11 patients completed a questionnaire at 24 months).

Table 18 Global health status scores for third-line patients participating in Study 301

| Arm | Baseline | 6 weeks | Months | | | | |
|---|---|---|---|---|---|---|---|
| | | | 3 | 6 | 12 | 18 | 24 |
| Eribulin third-line (n=158) | 55.2 (n=148) | 57.4 (n=118) | 60.9 (n=86) | 59.8 (n=46) | 64.2 (n=17) | 70.8 (n=6) | 83.3 (n=5) |
| Capecitabine third-line (n=151) | 55.2 (n-147) | 61.4 (n=122) | 61.0 (n=75) | 62.1 (n=44) | 60.8 (n=17) | 66.7 (n=9) | 68.1 (n=6) |

Source: CS, adapted from Figure 18 and company response to ERG clarification letter, A10

While no other HRQoL data that specifically relate to the third-line population are reported, the company states results from the third-line Study 301 patients are "consistent with those in the overall population" (CS, p102). The results for the overall population are presented on pp94 to 100 of the CS and summarised in the Appendices to this ERG report (Section 11.5, Table 40). Without equivalent data being presented for the third-line population, the ERG is unable to comment further on the HRQoL data.

No data for Subgroup 2 patients are available. Nevertheless, the QLQ-C30 results from Study 301 were converted into EQ-5D utility scores and used in the company's economic analysis (see Section 5.5.9).

## 4.9 Supporting safety data from observational studies

Since April 2011, eribulin has been made available to more than 2300 patients in England via the CDF. Therefore, in addition to the studies identified by its systematic review, the company were also able to present non-RCT, 'real world' evidence to support the assessment of the safety of eribulin. International studies were also identified. The company does not specify how these sources of observational data were identified or selected. The sources of supporting safety data supplied are:

- An audit of 108 patients treated with eribulin at the Royal Marsden Hospital in London, prospectively registered in a database between November 2011 and December 2013 (conference abstract and slides presentation)[37]
- An audit of 75 patients treated with eribulin via the North West CDF from August 2011 to March 2013 (conference abstract)[38]
- An audit of 25 patients treated at 22 centres with eribulin in London via the London CDF between September 2011 and February 2013 (published paper)[39]
- The EUFORIA-1 observational, transversal, retrospective, national study of 104 patients from 19 Spanish hospitals (13 public, 6 private) who were treated between April 2011 and March 2012 (poster presentation)[40]
- The ERIBEX retrospective, international, multi-centre study of 258 patients with LABC/MBC treated at three centres in France and one centre in Switzerland between 28 March 2011 and 15 January 2014 (published paper).[41]

The ERG has summarised data from these studies in Table 19. Patients included in the CDF audits had, on average, received ≥3 prior lines of chemotherapy for LABC/MBC whilst patients in the international studies had received four or five prior lines of chemotherapy for LABC/MBC. In all studies, ≥80% received previous treatment with capecitabine. Overall, the incidences of the most commonly reported key AEs were consistent with the incidences reported in the EMBRACE trial (see Section 4.4.2). In fact, in most cases, the frequencies of these key AEs in each study were lower than those reported for patients participating in the EMBRACE trial.

Table 19 Key safety data from observational studies and the EMBRACE trial

| Key study details, safety data and efficacy data | CDF audits (England) | | | International studies | | RCT |
|---|---|---|---|---|---|---|
| | Royal Marsden | North West CDF | London CDF | EUFORIA-1 | ERIBEX | EMBRACE (ITT population) |
| Number of patients on eribulin | 108 | 75 | 25 | 104 | 258 | 508 |
| Median age, years | 54 | 53 | 58 | 57 | 59 | 55 |
| Cycles | | | | | | |
| • Median | 5 | 6 | 4 | 4 | 5 | 5 to 6 |
| • Range | 1 to 14 | NR | 1 to 15 | 1 to 14 | 1 to 19 | 1 to 55 |
| • ≥5 cycles, % | 57 | 52 | NR | 42.3 | NR | 58.6 |
| Previous lines of chemotherapy for LABC/MBC | | | | | | |
| • Median | 3 | NR | 3 | NR | 4 | NR |
| • Range | 1 to 7 | 0 to 6<br>≤3: 70% | 1 to 4 | NR<br>≥5: 50.9% | 1 to 9 | NR<br>≥3: 86.6% |
| Patients who previously received capecitabine, % | 93 | 85 | 80 | 80.8 | 85 | 72.8 |
| Asthenia/fatigue, % | | | | | | |
| • All Grade | 65 | 55 | 8 | 44.2 | 60.9 | 53.7 |
| • Grade ≥3 | 7 | NR | NR | NR | NR | 8.7 |
| Neutropenia, % | | | | | | |
| • All Grade | 45 | 17 | 32 | 25 | 38.4 | 51.7 |
| • Grade ≥3 | 32 | NR | 0 | NR | 20.9 | 45.1 |
| Alopecia, % | | | | | | |
| • All Grade | 35 | NR | NR | 17.3 | 19.4 | 44.5 |
| • Grade ≥3 | NR | NR | NR | NR | NR | 0 |
| Peripheral Neuropathy, % | | | | | | |
| • All Grade | 28¥ | 33 | 20 | NR | 43.0 | 34.6 |
| • Grade ≥3 | 2¥ | NR | 4 | NR | 3.9 | 8.2 |
| Nausea, % | | | | | | |
| • All Grade | NR | 32 | 12 | 10.6 | 10.5 | 34.6 |
| • Grade ≥3 | NR | NR | NR | NR | NR | 1.2 |

AEs=Adverse events; CDF=Cancer Drugs Fund; ITT=intention-to-treat; NR=Not reported
†Reports data comparing patients where re-challenged with an anthracycline or a taxane versus those who were not *Time to treatment progression ¥Neurotoxicity
Source: CS, adapted from Table 35 and p119; additional data extracted from original sources

## *4.10 Conclusions of the clinical effectiveness section*

The company has reported evidence for the clinical effectiveness of two populations relevant to the review of TA250:

- All patients receiving ≥3 chemotherapy regimens for LABC/MBC (ITT population of the EMBRACE trial): patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable
- Subgroup 2: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated). Prior treatment also includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable.

Both populations are subgroups of the population for which eribulin is now licensed (as from 2014), namely: patients with LABC/MBC whose disease has progressed after at least one prior chemotherapeutic regimen for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. However, the ITT population addressed is the same as that for which eribulin was initially licensed (in 2011) and both populations are identical to the populations that were the focus of the TA250 FAD. The ERG considers this to be appropriate for a review of TA250.

Although the populations considered by the company are identical to those addressed during TA250, the comparator for Subgroup 2 patients is now TPC whereas, previously, the comparator on which the AC finally focussed was vinorelbine. The ERG agrees with the company's view that TPC is a pragmatic comparator for all patients receiving ≥3 chemotherapy regimens for LABC/MBC, including the Subgroup 2 population.

The primary clinical evidence source for this appraisal is the EMBRACE trial. This was a good-quality, multi-centre, phase III, open-label RCT that compared treatment with eribulin versus TPC. The trial population comprised 762 patients, most of whom had been heavily pre-treated (having received ≥3 previous regimens for LABC/MBC; ≥73% received previous treatment with capecitabine). Compared with TPC, this trial has demonstrated an improvement in median OS and median PFS for patients treated with eribulin in the ITT and Subgroup 2 populations. The ERG considers the primary and secondary outcome results to be robust. However, the company's OS hazard ratio for Subgroup 2 patients and the PFS hazard ratios for both the ITT and Subgroup 2 populations should be viewed with caution as the approach taken to calculate these values is only valid if the relevant K-M data are proportional to one another. Analyses carried out by the ERG suggest that the ITT

population PFS K-M data, the Subgroup 2 OS K-M data and the Subgroup 2 PFS K-M data are not proportional.

EMBRACE trial safety data and data from five supporting observational studies of heavily pre-treated patients (≥3 prior lines of chemotherapy for LABC/MBC; ≥80% received previous treatment with capecitabine) indicate that eribulin has an acceptable safety profile and is well tolerated (number of median cycles in the EMBRACE trial was reported to be between five and six and in the observational studies it was between four and six). There were no notable differences between the frequencies of AEs in the EMBRACE trial safety population and the frequencies in the Subgroup 2 population. The ERG considers that the EMBRACE trial and observational studies are likely to be generaliseable to NHS clinical practice.

HRQoL data are not available from the EMBRACE trial. The company has presented data from Study 301 for all patients and third-line patients. No patient received later lines of treatment and no patient had received previous treatment with capecitabine. Therefore, the generalisability of HRQoL data from Study 301 to the ITT population or Subgroup 2 patients may be questioned.

# 5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of prescribing eribulin for the treatment of LABC/MBC for patients whose disease has progressed following at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated), i.e. the group of patients labelled Subgroup 2 by the company.

The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has also provided an electronic copy of their economic model, which was developed in Microsoft Excel.

## *5.1 ERG comment on company's review of cost-effectiveness evidence*

### 5.1.1 Objective of cost effectiveness review

The company conducted a systematic review of published cost effectiveness studies relevant to the decision problem for Subgroup 2 patients on 23rd December 2015. Embase (via the Scopus platform), Medline and Medline In-Process (via the PubMed platform) and the Cochrane Library were searched from 1 January 2009 to 30 November 2015 and retrieved studies were restricted to those published in the English language. This search was supplemented by additional searching of the clinicaltrials.gov website on 12th February 2016 and proceedings from the ASCO, ESMO, AACR and International Society for ISPOR conferences on 23rd December 2016. Details of the search strategies employed by the company are provided in Appendix 2 to the CS.

### 5.1.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used by the company to facilitate study selection are reproduced in Table 20.

Table 20 Eligibility criteria used in company economics search strategy

| Parameter | Inclusion | Exclusion |
|---|---|---|
| Population | Adult patients AND<br>[MBC OR<br>Advanced breast cancer (ABC)] AND<br>3rd line plus | Non-human OR<br>Children OR<br>Adolescents OR<br>Males OR<br>First- and second-line |
| Intervention | Eribulin (monotherapy) | All other treatments |
| Comparator | Any | |
| Outcomes | All | |
| Study design | Cost OR Budget OR Budget impact OR Expenditure OR<br>Utilization OR Cost effectiveness OR Cost utility OR Cost benefit OR<br>Cost Minimization OR<br>Cost/Burden of illness studies OR<br>Resource utilisation | Editorials OR<br>Notes OR<br>Comments OR<br>Letters OR<br>Reviews OR<br>Abstracts without full paper available |
| Language | English | Non-English studies |

MBC=metastatic breast cancer
Source: CS, Table 38

### 5.1.3 Included and excluded studies

The company did not identify any cost effectiveness studies conducted from a UK perspective that were relevant to the Subgroup 2 population. Five cost effectiveness studies[42-45] were initially identified, including two from the grey literature. However, none of these five studies was considered by the company to fall within the final scope issued by NICE. Four studies were conducted outside of the UK (Tremblay,[39] Lopes,[40] Jones[41] and Dranitsaris[42]) and the fifth was the ERG's summary of NICE TA250.[29] The ERG agrees that the summary of NICE TA250[29] could be justifiably excluded from the review since the focus of the paper was not the Subgroup 2 population/comparator. The authors of this paper[29] do however note that: "A supplementary evidence submission from the manufacturer was considered" (p147), and the ERG considers that this evidence[46] is relevant to the Subgroup 2 analysis. There is therefore an argument for including this supplementary evidence submission[46] (and ERG critique of this evidence[47]) even though the clinical data are derived from an earlier data-cut from the EMBRACE trial than are now available.

### 5.1.4 Findings from cost effectiveness review

None. The company's literature search did not identify any cost effectiveness studies to support the use of eribulin for the treatment of LABC/MBC for patients whose disease has progressed following at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated).

## 5.2 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and is confident that there are no published cost effectiveness studies that fully meet the company's inclusion criteria. The databases searched and search terms used appear to be reasonable.

## 5.3 Summary of the company's submitted economic evaluation

The company has developed a de novo economic model to allow the comparison of the cost effectiveness of two treatment regimens for patients in Subgroup 2: eribulin and TPC (vinorelbine, gemcitabine, anthracyclines [doxorubicin] and taxanes [paclitaxel and docetaxel]). All patients in Subgroup 2 are assumed to have received prior treatment with capecitabine; therefore, TPC for Subgroup 2 patients excludes capecitabine.

### 5.3.1 Model structure

The cost effectiveness model presented by the company is based on a partitioned survival model comprising three mutually exclusive health states: pre-progression or stable disease, post-progression or progressive disease, and dead. All patients enter the model in the stable health state and remain in this state until disease progression. At the beginning of each time period patients can either remain in the same health state or move to a worse health state. For example, patients in the stable health state can move to the progressive health state or to the dead health state, whilst patients in the progressive health state can only move to the dead health state. The dead health state is the terminal state. A schematic of the company model is presented in the CS and reproduced in Figure 1.

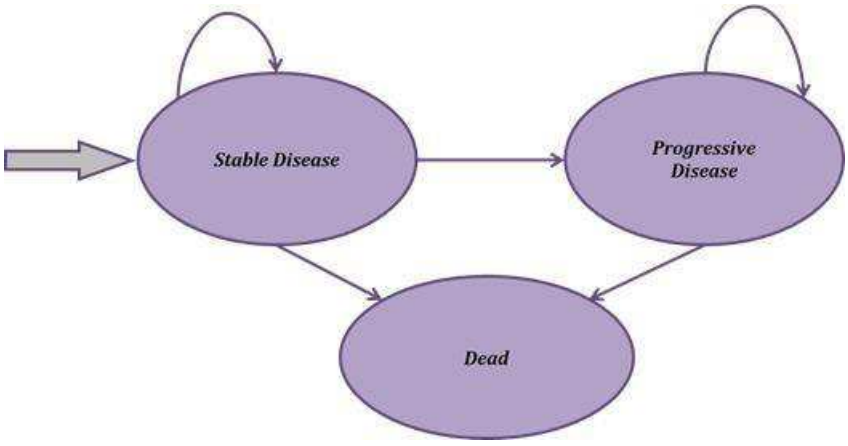


Figure 1 Company model structure

Source: CS, Figure 26

The PFS data represent the frontier between the health states of stable and progressive disease, whilst the OS data represent the frontier between the progressive disease and dead health states. Estimates of OS and PFS are based on K-M data from the EMBRACE trial. The model uses a cycle length of one month (30.42 days).

Treatment with the intervention or comparator begins when the patient enters the model in the stable health state and is assumed, in the base case, to continue until the patient has received the appropriate number of cycles of treatment (which vary depending on therapy) or until disease progression, whichever comes first.

### 5.3.2 Population

The population reflected in the company model is patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated), i.e. Subgroup 2. All patients in the company model have previously received capecitabine.

### 5.3.3 Interventions and comparators

**Primary treatments**

Eribulin is implemented in the model in line with the licensed dose, i.e. 1.23mg/$m^2$ administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle.

The base case comparator in the cost effectiveness analysis is TPC. The proportions of the different therapeutic options constituting TPC are taken from the ITT population in the EMBRACE trial, excluding capecitabine and any treatments that were used as initial treatment in less than 10% of the TPC arm. The proportions are therefore calculated on a subset of the TPC group. The treatment proportions for TPC are shown in Table 21 and these are used for both primary and subsequent lines of treatment.

The ERG received data on the actual initial treatments received by Subgroup 2 patients in the TPC arm during the clarification process. As these data were not sufficiently different to the proportions used in the base case analysis, no changes were made to the economic model.

The dosing of TPC depends on the chosen treatment. Investigators followed the instructions on the package insert, or local practice for drugs used off-label where the package instructions did not contain the relevant information.

Table 21 Proportions of Treatment of Physician's Choice

| Drug name | Number of patients | Proportion | |
|---|---|---|---|
| | | ITT population | Subgroup 2 |
| Vinorelbine | 61 | 24.00% | 36.75% |
| Gemcitabine | 46 | 18.10% | 27.71% |
| Paclitaxel | 26 | 10.20% | 15.66% |
| Doxorubicin | 23 | 9.10% | 13.86% |
| Docetaxel | 10 | 3.90% | 6.02% |
| Total | 166 | 65.30% | 100.00% |

ITT=intention-to-treat
Source: CS, Table 43 and The EMBRACE trial clinical study report, Table 10

In a scenario analysis, the company also considered a comparator arm in which patients, rather than being treated with TPC, were treated with either vinorelbine monotherapy (57%) or gemcitabine monotherapy (43%). In this scenario the relative treatment proportions were those observed in the ITT population of the EMBRACE trial.

**Secondary treatments**

Patients transitioning from the stable to progressive health states are assumed to receive secondary chemotherapy treatments in the proportions given in Table 21.

**Treatment duration**

In the base case, the maximum treatment duration in the model for patients in Subgroup 2 is set at 6 months. This includes all treatments received in both the stable and progressive health states (primary plus secondary treatments). The duration of any secondary treatment received in the progressive health state following treatment with either eribulin or TPC is therefore linked to the duration of the primary treatment in the stable health state. An alternative scenario is also presented in which patients receive initial treatment until disease progression and then do not receive any further treatments. Further details on the company's analysis of treatment duration are provided in Table 45 of the CS.

**Dose intensity**

Dose reductions and delays due to AEs are included in the model using a dose intensity modifier. Dose intensity for patients treated with eribulin is 0.84, based on the mean dose intensity observed for patients treated with eribulin in the ITT population of the EMBRACE trial. For simplicity, dose intensity for patients treated with TPC is assumed to be the same as that for patients treated with eribulin.

**Wastage**

Doses are calculated for each of the intervention and comparator drugs using a normal distribution of body surface area (BSA) and the licensed dose per $m^2$ of BSA. An estimate of 1.74$m^2$ for women with breast cancer in the UK (Sacco et al)[6] is used. The cost of any drugs wasted is included in the base case analysis.

The company also performed a scenario analysis in which drug wastage was minimised. A rounding rule was employed to adjust the calculated dose for any given BSA. This dose adjustment was based on 10% of the smallest pack size available for each drug. For example, the smallest pack size available for eribulin is 0.88mg and so the dose adjustment limit for eribulin is 0.08mg. A patient receiving treatment with eribulin who requires a dose of 1.85mg will receive a dose of 1.76mg (two 0.88mg packs) with no waste. A patient whose required eribulin dose is 1.86mg will receive their full dose from three 0.88mg packs and 0.78mg is wasted.

### 5.3.4 Perspective, time horizon and discounting

The company states that the cost effectiveness analysis is undertaken from the perspective of the NHS in England and Wales. The analysis excludes patients' out-of-pocket expenses, carers' costs and lost productivity derived costs. The time horizon in the base case is 5 years, with 10- and 20-year time horizons included as scenario analyses. Costs and benefits are discounted at a rate of 3.5% per annum.

### 5.3.5 Treatment effectiveness and extrapolation

The primary data source for the economic model is patient-level data from the EMBRACE trial. The data from this trial were very mature, with only 3% of the Subgroup 2 population in either arm still alive at the time of the 95% OS data cut for the ITT population (June 2013). Given the maturity of the available survival data, the company was able to use the K-M data directly to model OS and PFS for both eribulin and TPC in the base case using a 5-year time horizon.

For the 10- and 20-year time horizon scenario analyses, the company projected PFS and OS beyond the available K-M data by appending an exponential curve to the K-M data at 5 years. The company also investigated using a Weibull curve to project beyond 5 years, but concluded (as a result of visual inspection) that an exponential extrapolation was more appropriate.

**Alternative comparator (vinorelbine/gemcitabine monotherapy) scenario**

K-M survival data for this subgroup of the Subgroup 2 patients who participated in the TPC arm of the EMBRACE trial were identified. These data were used to represent transitions between health states in the 5-year base case. To model survival in this population for the 10 and 20 year scenarios, the 5-year K-M data were appended with either an exponential or Weibull distribution.

### 5.3.6 Health-related quality of life

HRQoL data were not collected as part of the EMBRACE trial and the company therefore conducted a literature search in order to identify HRQoL data relevant to the decision problem (details of which are provided in Appendix 2 to the CS and summarised in Appendices to this ERG report, Section 11.1). The model uses HRQoL data collected in Study 301 identified by this search. This phase III study was designed to compare the effectiveness of treatment with eribulin versus capecitabine in patients with LABC/MBC previously treated with an anthracycline and a taxane. HRQoL was assessed in Study 301 using the EORTC QLQ-C30 and mapped to EQ-5D derived utility scores using a published regression algorithm.[48] The EQ-5D utilities were constructed using the original UK tariff.[49]

The mapped utility values from patients on eribulin in Study 301 are used to represent the equivalent health states in this analysis. The aggregated utility value for the whole Study 301 population is used as the 'progressive' health state for both eribulin and TPC. The 'baseline' and 'tumour response' values for eribulin and TPC groups are considered separately and are adjusted in order to take into account differing rates of tumour response and AEs (see Table 22).

Table 22 Health state utility values

| Health state | Eribulin | TPC* |
|---|---|---|
| Baseline | 0.704 | 0.704 |
| Tumour response | 0.708 | 0.708 |
| Incremental utility of response | 0.076 | 0.076 |
| Tumour response rate | 12.2% | 4.7% |
| Disutility of AEs | -0.0071 | -0.0066 |
| Stable disease | 0.706 | 0.701 |
| Progressive disease | 0.679 | 0.679 |

AEs=adverse events; TPC=Treatment of Physician's Choice;
*TPC assumed equal to eribulin for baseline and tumour response utility values
Source: CS, Table 57

A linear mixed-effects model was used to predict the impact of specific AEs on utility scores from the EORTC QLQ-C30 data from Study 301 (see Table 23). Only common AEs (all grades with a prevalence ≥10%) or serious (≥3 with a prevalence ≥2%) are included within the model.

This disutility value is then multiplied by the prevalence of each AE over the entire treatment duration and is used to estimate a monthly AE rate for each arm of the trial. This value is then used to calculate an overall disutility for eribulin and TPC (see Table 22).

The linear mixed-effects model estimated an improvement in utility for alopecia; alopecia has a disutility of zero in the model. Alopecia and peripheral neuropathy are not part of the EORTC QLQ-C30 questionnaire and therefore these utility values should be interpreted with caution.

Table 23 Adverse event disutility values

| Health state | Disutility |
|---|---|
| Anaemia | -0.010 |
| Nausea | -0.021 |
| Neutropenia | -0.007 |
| Febrile neutropenia | -0.012 |
| Alopecia (all-Grade) | 0.000 |
| Leukopenia | -0.003 |
| Diarrhoea | -0.006 |
| Asthenia/fatigue | -0.029 |
| Peripheral neuropathy | -0.014 |
| Dyspnoea | -0.027 |
| Palmar-Plantar Erythro-Dysaesthesia Syndrome | 0.000 |

Source: CS, Table 51

The rates of AEs used by the company to calculate costs and effects differ. For utilities, Grade ≥3 AEs with prevalence greater than 2% are included, with the addition of alopecia, in line with feedback to the company from the ERG during TA250. For costs, an additional criterion of 'AEs that require treatment or hospitalisation' is also applied. The original data sources are difficult to determine within the model.

### 5.3.7 Resources and costs

**Drug costs**

The price of eribulin used in the model is the approved PAS price. The costs for the TPC arm are based on the proportions of each of the individual TPC treatment options used during the EMBRACE trial (Table 21). These proportions are replaced by a 50:50 weighting of the costs of vinorelbine and gemcitabine monotherapies in a scenario analysis.

Table 24 Drug acquisition costs per pack/vial

| Drug | Tablet dose/ vial concentration | Pack size/ vial volume | Cost per vial/pack | Source |
|---|---|---|---|---|
| Eribulin | Solution vial | 2ml (0.88mg) | [redacted] | CS |
| | | 3ml (1.32mg) | [redacted] | |
| Vinorelbine (oral) | Soft capsules | 10 capsules x 20mg | £439.80 | MIMS[50] |
| | | 10 capsules x 30mg | £659.80 | |
| | | 10 capsules x 80mg | £1,759.20 | |
| Vinorelbine (IV) | Solution vial | 10mg | £5.04 | eMIT[51] |
| | | 50mg | £18.24 | |
| Capecitabine | Tablets | 60 tablets x 150mg | £7.73 | eMIT[51] |
| | | 120 tablets x 500mg | £29.59 | |
| Gemcitabine | Powder vial | 200mg | £3.99 | eMIT[51] |
| | | 1000mg | £30.89 | |
| | | 2000mg | £21.39 | |
| Docetaxel | Solution vial | 20mg | £4.92 | eMIT[51] |
| | | 80mg | £12.47 | |
| | | 160mg | £34.83 | |
| Paclitaxel | Solution vial | 30mg | £3.41 | eMIT[51] |
| | | 100mg | £8.50 | |
| | | 150mg | £11.50 | |
| | | 300mg | £21.48 | |
| Doxorubicin | Solution vial | 10mg | £1.53 | eMIT[51] |
| | | 50mg | £4.04 | |
| | | 200mg | £20.30 | |

IV=intravenous; eMIT=electronic Medicines Information Tool; CS=company submission
Source: CS, Table 69

The subsequent treatment costs following disease progression are the same as the TPC initial treatment costs for both arms of the trial.

**Administration costs**

Administration costs for eribulin and each of the TPC treatment options are shown in Table 25. Paclitaxel is considered to be a complex chemotherapy due to the long infusion time associated with this treatment.

All chemotherapy is considered part of ongoing therapy, eliminating the need for separate initial and subsequent Healthcare Resource Group (HRG) codes.

Table 25 Cost of administration

| Treatment | Type of administration | Currency code | Cost per administration | Source |
|---|---|---|---|---|
| Capecitabine & oral vinorelbine | Deliver exclusively oral chemotherapy | SB11Z | £171.10 | NHS Reference Costs 2014/15[52] |
| Eribulin, gemcitabine, docetaxel & doxorubicin | Deliver simple parenteral chemotherapy at first attendance | SB12Z | £239.12 | NHS Reference Costs 2014/15[52] |
| Paclitaxel | Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance | SB14Z | £389.41 | NHS Reference Costs 2014/15[52] |

Source: CS, adapted from Table 63

**Direct medical costs**

The costs of monitoring patients receiving eribulin and chemotherapy and the cost of care at the end of life are provided in Table 26. Supportive palliative care costs are assumed to be necessary in the final 6 months of life. End of life costs are attributable to the 2-week period prior to death and the total cost is weighted according to the proportion of people likely to spend this time in each place of care.

Computed tomography scans and community nurse home visits are not assumed to be necessary for all patients.

Table 26 Direct medical costs

| Type of cost | Health state | Cost | Usage | Source |
|---|---|---|---|---|
| Stable and progressive disease costs | | | | |
| Medical oncologist – follow-up | Stable & progressive disease | £158.54 | | NHS Reference Costs 2014/15[52] |
| GP contact | | £44.00 | | PSSRU 2015[53] |
| CT scan | | £92.03 | 33% usage assumed | NHS Reference Costs 2014/15[52] |
| Supportive palliative care costs | | | | |
| Medical oncologist – follow-up | Progressive disease (6 markov cycles prior to transitioning to "Dead" health state) | £158.54 | | NHS Reference Costs 2014/15[52] |
| GP home visit | | £44.00 | | PSSRU 2015[53] |
| Clinical nurse specialist | | £88.00 | | |
| Community nurse home visit | | £58.00 | | |
| End of life costs | | | | |
| Hospital/medical institution | Progressive disease (0.5 markov cycles prior to transitioning to "Dead" health state) | £5135.25* | Assumed to apply to 40% of patients | NICE Breast Cancer Guidance (2009), Marie Curie report on End of Life Costs[a] |
| Hospice | | £6402.15* | Assumed to apply to 10% of patients | |
| At home (with community support) | | £2649.47* | Assumed to apply to 50% of patients | |

Source: CS, adapted from Table 64

*Inflated to 2014-2015 using PSSRU 2015,[53] The hospital & community health services (HCHS) index for 2014, Table 16.3 (Pay + prices); [a] Actual source not stated in CS

**Adverse event costs**

The costs of AEs are detailed in Table 27.

The company assumes there is only one episode of any single AE for each affected patient; this could lead to a large underestimation of the true AE costs. No further information on the duration or the severity of the AEs is included in the CS.

Table 27 Adverse event costs

| | Cost per episode (£) | HRG code | Description |
|---|---|---|---|
| Anaemia | 516.55 | SA04K | Iron deficiency anaemia with CC Score 2 to 5 (non-elective short stay) |
| Nausea | 399.42 | JA12L | Malignant breast disorders without Interventions, with CC Score 0 to1 (non-elective short stay) |
| Neutropenia | 127.7 | XD25Z | Neutropenia drugs band 1 |
| Febrile neutropenia† | 6060 | PA45Z (2012-2013) | Febrile neutropenia with malignancy |
| Alopecia (all-Grade) | 0 | | Assumption - no cost |
| Leukopenia | 127.7 | XD25Z | Neutropenia drugs band 1 |
| Diarrhoea | 399.42 | JA12L | Malignant breast disorders without Interventions, with CC Score 0 to1 (non-elective short stay) |
| Asthenia/fatigue | 38 | N/A | 1hr community nurse visit per day for duration of adverse event |
| Peripheral neuropathy† | 146.33 | AB05Z (2013-2014) | Procedures in outpatient Intermediate pain procedures |
| Dyspnoea | 490 | DZ20E | Pulmonary oedema without Interventions, with CC Score 6+ |
| Palmar-Plantar Erythro-Dysaesthesia Syndrome | 429.65 | JD07J | Skin Disorders without Intervention, with cc score 2 to5 (non-elective inpatient short stay) |

CC=with complications; HRG=Healthcare Resource Group
†Inflated to 2014-2015 using PSSRU 2015,[53] The hospital & community health services (HCHS) index for 2014, table 16.3 (Pay + prices)
Source: CS, Table 66

### 5.3.8 Cost effectiveness results

Total costs, life years gained (LYG), QALYs and incremental costs per QALY gained for the cost effectiveness comparison of treatment with eribulin versus TPC are shown in Table 28. In the base case, eribulin generates more benefits than TPC [redacted] LYG and +[redacted] QALYs) at an increased cost of [redacted]. The company base case incremental cost effectiveness ratio (ICER) for eribulin versus TPC is £35,624 per QALY gained.

Table 28 Base case cost effectiveness results

| | Total | | | Incremental | | | ICER per QALY gained |
|---|---|---|---|---|---|---|---|
| **Technologies** | **Costs** | **LYG** | **QALYs** | **Costs** | **LYG** | **QALYs** | |
| Eribulin | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £35,624 |
| TPC | [redacted] | [redacted] | [redacted] | | | | |

TPC=Treatment of Physicians' Choice; LYG=life years gained; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, Table 72

A summary of the predicted drug, drug administration and direct medical costs is presented in Table 29. Just over three-quarters of the difference in costs between the intervention and comparator technologies is due to differences in the cost of the primary therapy (eribulin or TPC).

Table 29 Summary of predicted resource use by category of cost

| Item | Therapy | | Increment | Absolute increment (£) | Absolute increment (%) |
|---|---|---|---|---|---|
| | Eribulin | TPC | | | |
| **Drug and administration costs** | | | | | |
| Primary therapy | [redacted] | [redacted] | [redacted] | [redacted] | 76.79% |
| Secondary therapy (TPC) | [redacted] | [redacted] | [redacted] | [redacted] | 0.04% |
| Administration | [redacted] | [redacted] | [redacted] | [redacted] | 9.75% |
| [redacted] | | | | | |
| Medical | [redacted] | [redacted] | [redacted] | [redacted] | 10.44% |
| Palliative care | [redacted] | [redacted] | [redacted] | [redacted] | 1.37% |
| End of life | [redacted] | [redacted] | [redacted] | [redacted] | 2.31% |
| Adverse events | [redacted] | [redacted] | [redacted] | [redacted] | 3.91% |
| **Total costs** | [redacted] | [redacted] | [redacted] | [redacted] | **100.00%** |

TPC=Treatment of Physicians' Choice
Source: CS, Table 78

### 5.3.9 Sensitivity analyses

**Deterministic sensitivity analyses**

Cost effectiveness results from nine different scenarios are presented in the CS and summarised in Table 30. These results are also displayed in a Tornado diagram (see Figure 2). The resultant ICERs range from £31,226 to £46,912 per QALY gained, i.e. ranging from £4,398 less than the base case to £11,288 greater than the base case.

Table 30 Results of deterministic sensitivity analysis

| Scenario | Parameter | ICER per QALY gained | |
|---|---|---|---|
| | | Lower value | Upper value |
| Base case | | | £35,624 |
| 1 | Benefits discount rate (0% and 6%) | £33,326 | £37,225 |
| 2 | Costs discount rate (0% and 6%) | £35,037 | £36,518 |
| 3 | Costs and benefits discount rate (0% and 6%) | £34,162 | £36,641 |
| 4 | Eribulin price (±20%) | £31,226 | £40,022 |
| 5 | Comparator price (±20%) | £35,401 | £35,848 |
| 6 | Administration costs (±20%) | £34,930 | £36,319 |
| 7 | Direct healthcare costs (±20%) | £34,947 | £36,302 |
| 8 | Prevalence of AEs (±20%) | £35,346 | £35,903 |
| 9 | HRG costs of AEs (±20%) | £34,447 | £46,912 |

AE=Adverse event; HRG=Healthcare Resource Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS p191 and Table 82

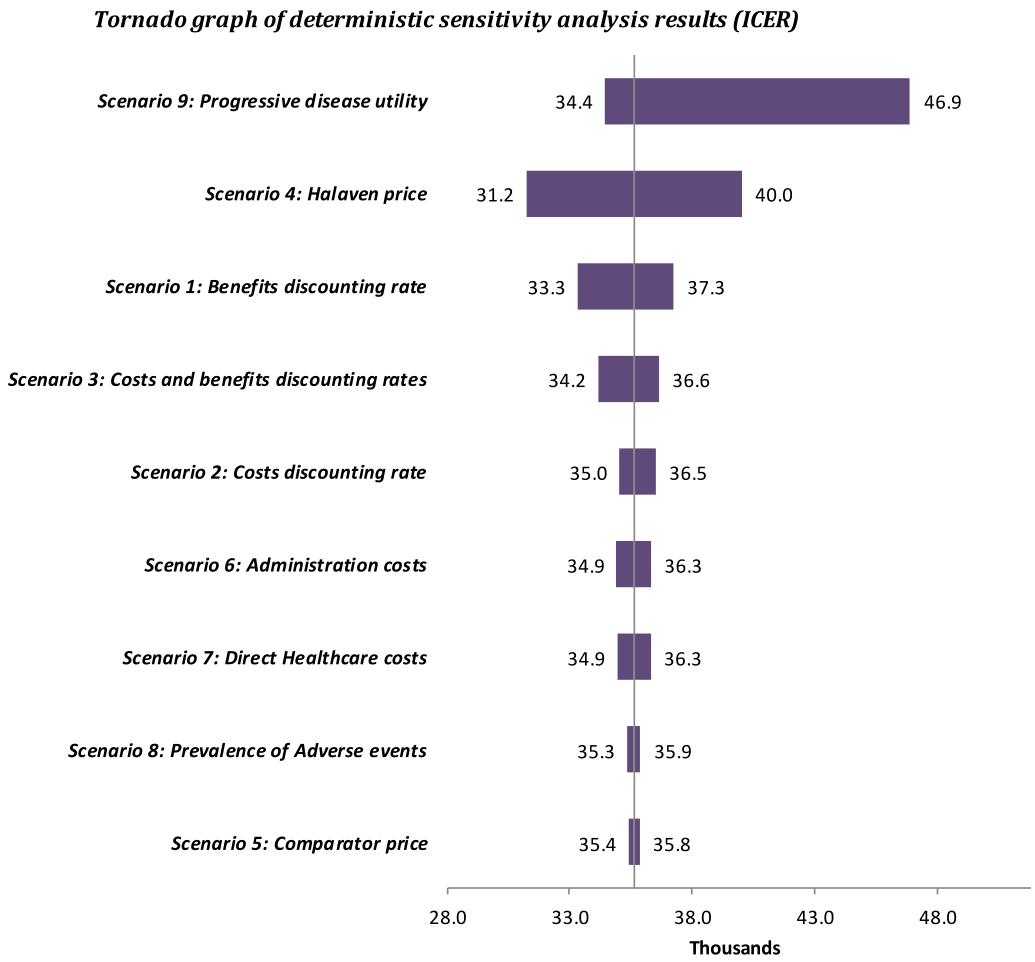


Figure 2 Deterministic sensitivity analysis results displayed in a tornado diagram

Source: CS, Figure 48

**Probabilistic sensitivity analyses**

The company's probabilistic sensitivity analysis (PSA) involved varying only a limited number of parameters (utility [baseline, tumour response and disease progression]), primary and secondary therapy drug costs, and survival [stable disease, progressive disease and end of life]).

The cost effectiveness plane and the cost effectiveness acceptability curves for Subgroup 2 patients are displayed in the CS and reproduced in Figure 3 and Figure 4 respectively. Results from the company's PSA show that, for Subgroup 2 patients, for the comparison of eribulin versus TPC, the ICERs per QALY gained range from between £20,000 to £60,000. Results also show that, for this treatment comparison, there is a 30% probability of treatment with eribulin being cost effective at a threshold of £30,000 per QALY gained and a 72% probability of eribulin being cost effective at a threshold of £50,000 per QALY gained.

Figure 3 Cost effectiveness plane

Source: Company model

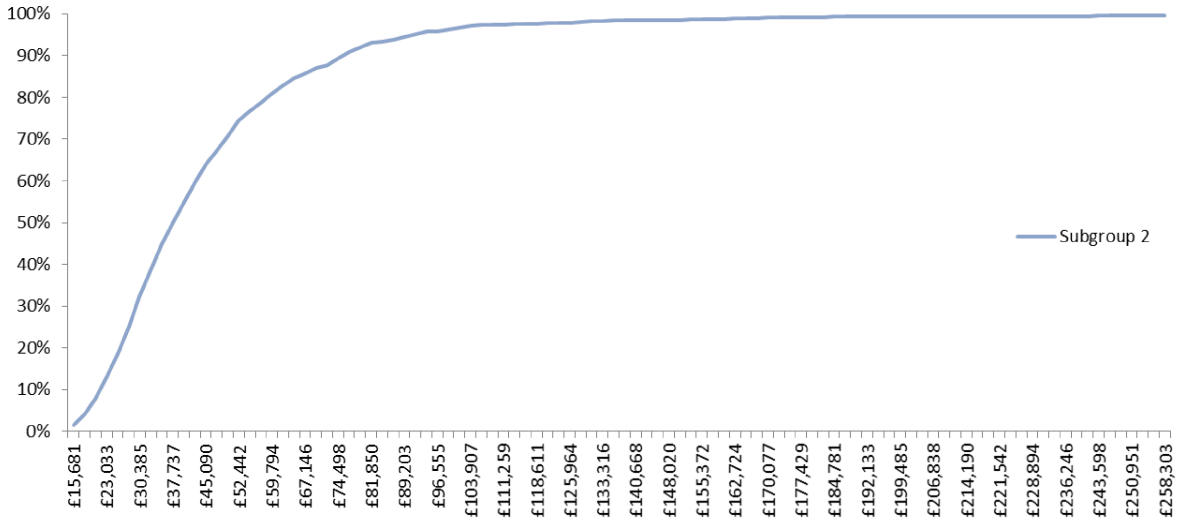


Figure 4 Cost effectiveness acceptability curve

Source: Company model

### 5.3.10 Scenario analyses

The company carried out six scenario analyses. Results from these analyses are presented in Table 31. The biggest effect on the company's base case cost effective result occurred when the cost of wastage was excluded from the company's base case calculations. This lowered the ICER per QALY gained for the comparison of eribulin versus TPC to £16,053 per QALY gained (a 54% reduction in the base case result).

Table 31 Scenario analysis results

| Scenario | Incremental | | | ICER per QALY gained |
|---|---|---|---|---|
| | LYG | QALY | Cost | |
| Base case | [redacted] | [redacted] | [redacted] | £35,624 |
| Maximum treatment duration threshold of 12 months | [redacted] | [redacted] | [redacted] | £39,164 |
| Excluding wastage | [redacted] | [redacted] | [redacted] | £16,053 |
| Vinorelbine and gemcitabine as comparator | [redacted] | [redacted] | [redacted] | £23,931 |
| Prevalence of AEs Grade ≥3 | [redacted] | [redacted] | [redacted] | £35,964 |
| Time horizon 10 years | [redacted] | [redacted] | [redacted] | £32,362 |
| Time horizon 20 years | [redacted] | [redacted] | [redacted] | £32,282 |

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life year
Source: CS, Table 84

### 5.3.11 Model validation and face validity check

The company took a number of steps to try to ensure the validity of the extrapolations and parameter values employed in their model:

- Trial survival data were used directly in the base case (5-year time horizon) analysis. To generate results for the 10-year and 20-year time horizon scenarios, the company employed the Tremblay et al[42] decision making criteria (which are based on the NICE Decision Support Unit document on survival extrapolations[54]) to select approaches to extrapolate the available trial survival data
- Costs were primarily based on the NICE Advanced Breast Cancer guidelines[8] and the most recent NHS Reference Costs (2014 to2015)[52]
- Utility and disutility values used in the model were kept as conservative as possible
- AE costs were based on a HRG/ Diagnosis-related group (DRG) approach
- Grade ≥3 AEs with a prevalence of greater than 2% were included in the analyses to ensure the inclusion of all important AEs and to facilitate consistency with the approach taken by the company to estimate disutilities.

The company's internal health economics and outcome research experts, as well as an external health economist, carried out quality control. An expert from the University of Glasgow validated the company's survival extrapolations.

## *5.4 Model checklists*

### 5.4.1 NICE reference case checklist

Table 32 NICE Reference case checklist completed by ERG

| Attribute | Reference case | Does the de novo economic evaluation match the reference case? |
|---|---|---|
| Decision problem | The scope developed by the Institute | Yes |
| Comparator(s) | Alternative therapies routinely used in the NHS | Treatment of physician's choice (a range of different alternative treatments) |
| Perspective costs | NHS and Personal Social Services | NHS costs only |
| Perspective benefits | All health effects on individuals | Yes |
| Form of economic evaluation | Cost effectiveness analysis | Yes |
| Time horizon | Sufficient to capture differences in costs and outcomes | Yes |
| Synthesis of evidence on outcomes | Systematic review | The company uses data from the EMBRACE trial, the only trial identified by the company's systematic review. This is appropriate |
| Outcome measure | Quality adjusted life years | Yes |
| Health states for QALY | Described using a standardised and validated instrument | No. Disease-specific quality of life trial data from another trial was converted by a generic mapping algorithm to approximate EQ-5D values |
| Benefit valuation | Time-trade off or standard gamble | Mapped onto time-trade off scale |
| Source of preference data for valuation of changes in HRQoL | Representative sample of the public | Indirectly |
| Discount rate | An annual rate of 3.5% on both costs and health effects | Yes |
| Equity | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes |
| Sensitivity analysis | Probabilistic sensitivity analysis | PSA lacks the facility to include correlated parameter values |

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; PSA=probabilistic sensitivity analysis

### 5.4.2 Drummond checklist

Table 33 Critical appraisal checklist for the economic analysis completed by the ERG

| Question | Critical appraisal | ERG comment |
|---|---|---|
| Was a well-defined question posed in answerable form? | Yes | |
| Was a comprehensive description of the competing alternatives given? | Yes | The range of currently used alternative therapies is included in the TPC combined comparator |
| Was the effectiveness of the programme or services established? | Yes | Clear evidence of survival gain in the defined population was established |
| Were all the important and relevant costs and consequences for each alternative identified? | Yes | |
| Were costs and consequences measured accurately in appropriate physical units? | Yes | |
| Were the cost and consequences valued credibly? | Not always | Several errors were identified (see Section 5.6) |
| Were costs and consequences adjusted for differential timing? | Partial | ERG corrected a minor error in method of discounting used |
| Was an incremental analysis of costs and consequences of alternatives performed? | Yes | |
| Was allowance made for uncertainty in the estimates of costs and consequences? | Partial | Deterministic sensitivity analysis was reported, but the PSA lacked the facility to include correlated parameters |
| Did the presentation and discussion of study results include all issues of concern to users? | Yes | Yes; all issues of concern to users were discussed |

ERG=Evidence Review Group; TPC=Treatment of Physicians' Choice

## *5.5 Critique of cost effectiveness analyses*

### 5.5.1 Design structure and implementation of the company model

The decision model submitted by the company is designed as a partitioned survival model (though some features are occasionally described as though it were a Markov model). The model is implemented as a Microsoft Excel workbook. It has been structured in an inconsistent manner, which increases the complexity of the logic and provides scope for error. The model features individual monthly cycles at the end of which patient status, resource use and costs are updated. However, all the treatments included in the model are prescribed on either a weekly or 3-weekly basis. For accuracy, it would have been preferable to employ weekly cycles, but 3-weekly cycles would also have been a reasonable alternative. In addition, in some parts of the model time conversions are based on 365 days per year, but elsewhere 365.25 days is used (including leap years). This difference is small but can accumulate over a lifetime horizon.

### 5.5.2 Patient survival and disease progression

The ERG submitted a clarification request for detailed K-M analysis results for OS, PFS and post-progression survival (PPS) from the EMBRACE trial and the company provided these data. The ERG also requested similar information for time to treatment discontinuation to allow the ERG to employ an alternative approach to estimating treatment costs. Unfortunately, this request was misinterpreted and the ERG could not use the results provided by the company.

**Overall survival**

The OS K-M data from the EMBRACE trial (Figure 5) indicate that, for patients in both the eribulin and TPC arms, the trial data are nearly complete (only two patients randomised to receive eribulin and one patient randomised to receive TPC were still alive at the time of data cut-off). Re-running the K-M OS analysis indicates that, without any projection of estimated survival in either arm to compensate for the missing follow-up data, the accurate value for the mean OS gain attributable to treatment with eribulin compared to TPC is 3.39 months (95% CI 0.83 to 5.96 months).

The company calibrated exponential projective functions to OS data from each trial arm and applied the results to both arms from month 60 onwards. The ERG has adopted a different approach, namely examining the trends in cumulative hazard plots of the trial data and identifying the time point in each trial arm where a long-term exponential trend becomes established – month 35 in the eribulin arm and month 27 in the TPC arm. The ERG then

applied the calibrated trend lines from the time closest to the final recorded trial death (month 64 for eribulin and month 56 for TPC).

An examination of Figure 5 highlights that, compared with the company's projection, the ERG's method of projection leads to a greater long-term OS advantage for patients treated with eribulin compared with TPC. As a result, implementing the ERG method in the model results in a small reduction of £199 per QALY gained in the size of the estimated ICER.

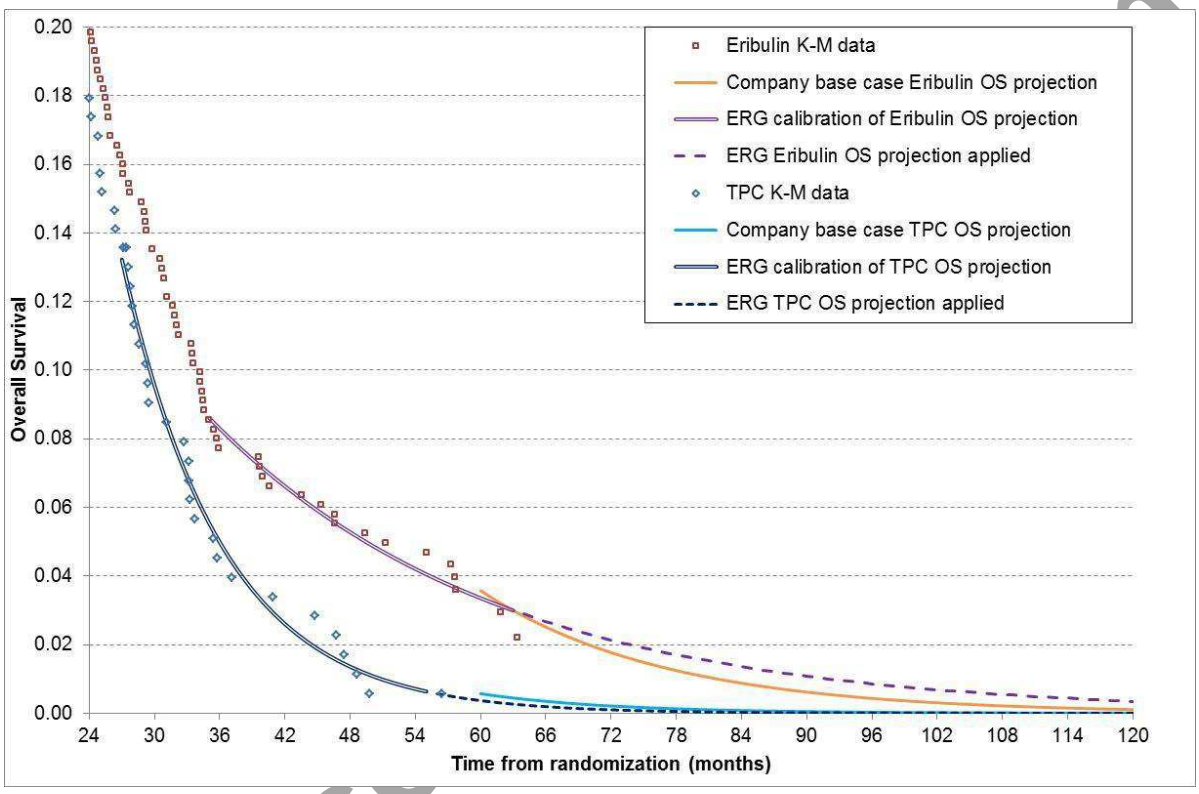


Figure 5 Overall survival Kaplan-Meier data from the EMBRACE trial and two approaches to survival projection

**Progression-free survival**

The company has fitted Weibull parametric curves to both sets of trial data, extending non-zero PFS values well beyond the maximum time at which patients were observed to remain progression-free (23 and 25 months), and replaced all of the K-M trial PFS data with the modelled alternative estimates.

Examination of the PFS K-M data from the EMBRACE trial (Figure 6) indicates that the trial data are complete for patients in both arms of the trial. There is, therefore, no need to carry out any projective modelling of PFS and so the ERG has used the K-M data directly. Re-running the K-M PFS analysis indicates that the accurate value for the mean PFS gain attributable to eribulin compared to TPC is 40.4 days (95% CI 13.0 to 67.8 days). However, the company base case results suggest a difference of just 8.2 days. When the ERG replaces the company Weibull curves with the original trial PFS data, the model estimated PFS gain increases to 40.2 days (95% CI 13.0 to 67.8 days).

The main effect of this ERG modification to the company model is to change the balance of treatment costs, so that the incremental cost rises, leading to an increase in the ICER per QALY gained of £1,557.

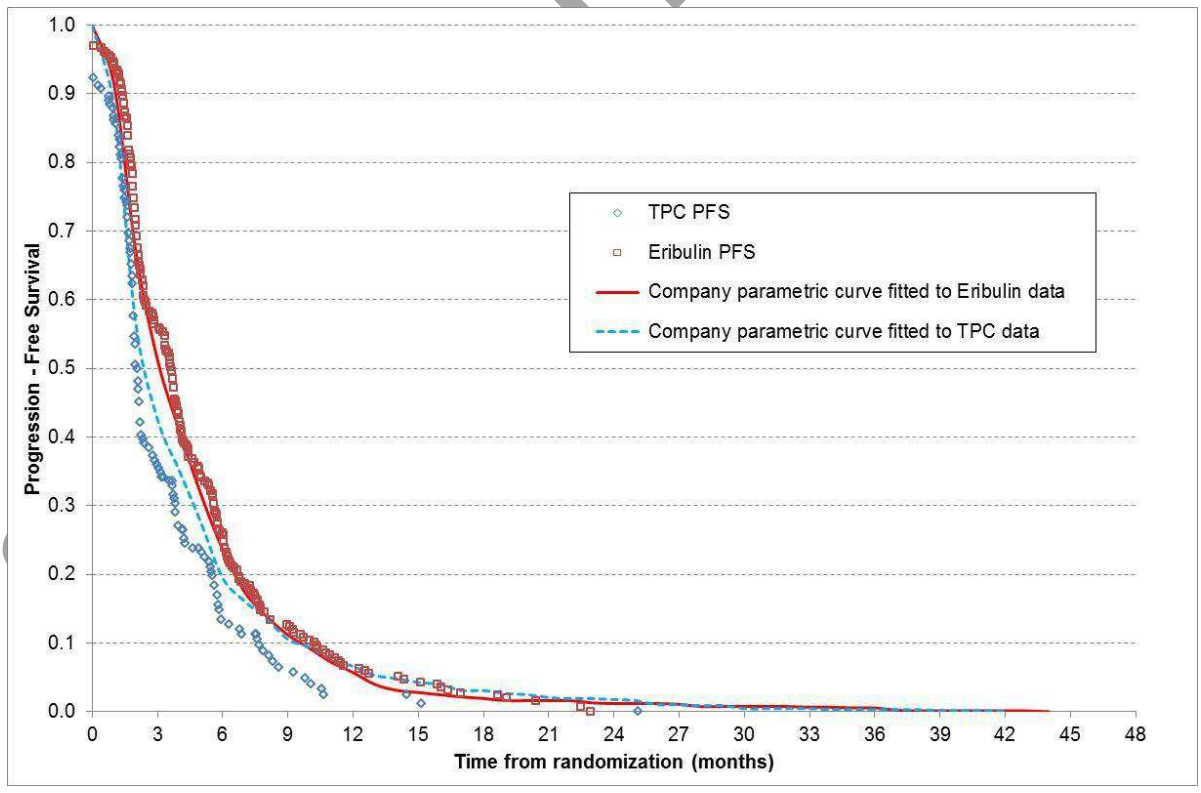


Figure 6 Progression-free survival Kaplan-Meier data from the EMBRACE trial and company Weibull parametric curves

**Post-progression survival**

Examination of the PPS K-M data from the EMBRACE trial, which was provided by the company in response to a clarification request, has led the ERG to have serious doubts as to the reliability of the provided data. Post-progression survival analysis includes only those patients whose 'progression event' was a non-fatal progression i.e. excluding any patients who died prior to the time of disease progression. Since the full complement of randomised patients has been included in each trial arm, it is clear that these analyses include patients who died without disease progression. As a result, it is not possible to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression.

However, the estimates described above for OS and PFS give strong support to a substantial gain in mean survival being experienced by some patients even after recorded disease progression and the cessation of eribulin treatment. This is an important finding, since evidence for many other cancer treatments shows that after progression previous treatments quickly cease to have any bearing on future survival prognosis.

### 5.5.3 Logic error

An important logic error has been identified in the company model. This relates to the calculation of the cost of treatment with oral vinorelbine. This results in a very low estimate for the cost of this drug being applied to the comparator arm of the model and, consequently, an excessive incremental cost being used to estimate the ICER per QALY gained for eribulin versus TPC. When this error is corrected, the base case ICER is reduced from £35,624 to £31,276 per QALY gained.

### 5.5.4 Acquisition cost of chemotherapy

The company has estimated the cost of chemotherapy drugs dosed in terms of BSA using UK BSA estimates from survey data.[55] However, the company modellers have confused standard error and standard deviation when calculating the costs of chemotherapy dosed according to BSA. In addition, no account has been taken of the therapeutic intent of the treatments included in the survey data.[55] This information is included in the full data set, available as a download from the journal web-site.[56] The ERG has selected only survey breast cancer patients whose treatment intent is not listed as adjuvant, neo-adjuvant or palliative, as the closest survey subset to the patients treated in the EMBRACE trial. This yields a slightly higher mean BSA (1.7448) and a standard deviation of 0.1785 (standard error 0.00924). All relevant chemotherapy treatment costs have been re-estimated by the ERG and compared with those used in the company model (Table 34).

The unit cost per dose of chemotherapy has been substantially underestimated for eribulin, oral vinorelbine (after the first cycle) and capecitabine, with smaller differences for all other agents.

Table 34 Unit costs of chemotherapy treatments, comparing ERG estimates to company model parameter values (after the company logic error has been corrected)

| Treatment | Unit | Company model | ERG estimate | Difference (ERG vs company model) |
|---|---|---|---|---|
| Eribulin | Per dose | [redacted] | [redacted] | +£176.65 (+44.2%) |
| Vinorelbine oral (cycle 1) | Per dose | £242.02 | £241.20 | -£0.82 (-0.3%) |
| Vinorelbine oral (cycle 2+) | Per dose | £242.02 | £315.84 | +£73.82 (+30.5%) |
| Vinorelbine (IV) | Per dose | £18.24 | £18.83 | +£0.59 (+3.2%) |
| Gemcitabine | Per dose | £29.14 | £26.20 | -£2.96 (-10.1%) |
| Docetaxel | Per dose | £34.83 | £27.90 | -£6.93 (-19.9%) |
| Paclitaxel | Per dose | £21.47 | £26.44 | +£4.97 (+23.1%) |
| Doxorubicin | Per dose | £9.62 | £11.48 | +£1.86 (+19.3%) |
| Capecitabine | Per cycle | £24.17 | £37.01 | +£12.84 (+53.1%) |

ERG=Evidence Review Group; IV=intravenous

### 5.5.5 Dose intensity

The company model features a parameter to represent dose intensity as measured in the EMBRACE trial. However, this does not have any effect on the estimated cost of treatments, nor on the company base case ICER per QALY gained. The cost of treatment is only affected when the company's alternative mode of calculating drug costs (without wastage) is employed.

### 5.5.6 Dose capping

Within the company model, the number of patients continuing on therapy is estimated using the company's PFS estimate. However, a close examination of the company logic indicates that the long-term PFS data included in the model are set to zero for all time periods after 43 months for the eribulin arm and after 41 months for the comparator arm. This arbitrary measure results in a small bias leading to a slightly higher estimated ICER per QALY gained. Applying the ERG's preferred PFS K-M data removes this bias.

### 5.5.7 Probabilistic sensitivity analysis

The company model includes a facility to carry out PSA. However, the model does not generate a probabilistic estimated ICER per QALY gained that can be compared with the deterministic ICER per QALY gained. The PSA in the company model cannot be considered to be a true PSA since it lacks any facility to incorporate uncertainty related to correlated parameter values, such as are present in the utility values estimated from Study 301 data, and the pre- and post-progression estimates based on regression coefficients. Moreover, drug cost estimates are only varied by a crude +/- 10% variation, an approach that is more akin to deterministic sensitivity analysis than PSA. As a result, the ERG does not consider that the PSA routines included in the company model provide any useful or reliable evidence as to the impact of parameter uncertainty. However, a PSA ICER per QALY gained calculated by the ERG from the random iteration data is very similar to the deterministic ICER per QALY gained.

### 5.5.8 Discounting

In the company model discounting of costs and outcomes is applied on a continuous basis, rather than annually in line with NHS budgeting and accounting years. This has the effect of increasing the incremental QALYs more than the incremental cost. Correcting this error has the effect of reducing the company base case deterministic ICER per QALY gained by approximately £154.

### 5.5.9 Health-related utility values

The company has applied a mapping algorithm, published by Crott and Briggs in 2010,[48] to estimate EQ-5D values from the QLQ-C30 quality of life questionnaire administered to patients in Study 301. The algorithm was based on data made available from an historical clinical trial, which recruited patients from 1999 and compared two chemotherapy regimens. The published trial results[57] indicate that only untreated patients with locally advanced (but not metastatic) breast cancer and good performance status were recruited, and only neo-adjuvant treatments were administered. The contrast between the EMBRACE trial and the trial upon which Crott and Briggs[48] based their utility mapping exercise must raise serious questions about the appropriateness of applying this reported algorithm to generate utility values for patients receiving third-line chemotherapy after two prior episodes of disease progression.

The alternative, previously considered by the ERG during TA250, is a utility value set published by Lloyd[30] specifically for breast cancer patients receiving chemotherapy using the Standard Gamble methodology. The utility values estimated by this method for stable disease and patients responding to treatment are quite similar to the values used in the company model. However, a very large discrepancy is observed for patients in the progressive disease health state; 0.68 in the company model compared to 0.496 from the Lloyd[30] analysis. It is particularly remarkable that the value used in the model for patients with stable disease (but not responding to treatment) is very similar to the value for progressed disease (0.69 versus 0.68), which the ERG considers implausible.

The ERG has tested the effect of substituting the Lloyd[30] progressive disease utility value in place of the company's preferred estimate, and can confirm a resulting increase in the size of the estimated ICER of more than £11,000 per QALY gained.

### 5.5.10 Subsequent lines of chemotherapy

The company model offers two options for the estimation of the cost of further lines of chemotherapy beyond eribulin or TPC as third-line therapy:

- Limiting the number of cycles of therapy overall (in the base case to no more than six cycles).
- "Treat to progression", which means that nobody who progresses alive whilst on eribulin or TPC incurs the costs associated with any subsequent chemotherapy (4th, 5th, etc lines of treatment).

Each of these approaches leads to anomalous results. The first option completely ignores an important component of differential costs – that patients who respond better to third-line treatment will, on average, continue third-line therapy for longer and may subsequently have a better performance status leading to a greater probability of proceeding to further lines of treatment. The second option effectively caps the cost of all subsequent treatments, which results in a bias in favour of eribulin which has been shown to lead to additional mean PPS time and therefore to more use of additional lines of treatment with their associated costs. It should be noted that these options relate only to the estimated cost of subsequent treatments, and have no effect on estimated survival gain or additional QALYs.

The ERG has developed a modification of the company model to provide a third option. This involves two changes:

1) The company cap on the maximum number of cycles (months) of further treatment is effectively removed by resetting the model cycle limit from six to 600.
2) The company references a study by Kantar Health[58] which shows the proportion of breast cancer patients progressing between lines of therapy from first to fifth lines. The ERG has calculated the proportion of patients suffering a non-fatal progression event that go on to receive an extra course of treatment; this ranges from 54% to 66%. The ERG has, therefore, amended the company model to estimate the costs of such care for 60% of the patients still alive in the progressed health state each month.

Applying this modification results in an increase in the incremental cost per patient of £1,600 and an increase in the size of the deterministic ICER of about £9,800 per QALY gained.

### 5.5.11 Logic error in calculation of eribulin administration costs

The ERG has identified a logical anomaly that can result in doses of eribulin being given to patients after month 6 but with no corresponding administration cost being calculated. When this error is corrected, the incremental cost of treatment with eribulin versus TPC increases by £670, and the company's base case ICER increases by more than £4,000 per QALY gained.

# 6 IMPACT ON THE ICER OF ADDITIONAL ERG ANALYSES

To address the points raised in Section 5, the ERG has made the following nine changes to the submitted company model:

- use of ERG preferred PFS estimates (R1)
- use of ERG preferred OS estimates (R2)
- use of annual rather than continuous discounting (R3)
- correction of logic error in costing oral vinorelbine (R4)
- use of ERG revised unit cost of eribulin (R5)
- use of ERG revised unit costs of comparator drugs (R6)
- use of ERG alternative utility value for progressed disease (R7)
- use of ERG method for estimating subsequent therapy costs (R8)
- correction of logic error in calculating eribulin administration costs (R9)

The three most influential ERG changes are the choice of utility value for the progressive disease health state (R7), the revised estimate of the cost of eribulin treatment (R5), and the method used to cost subsequent lines of treatment (R8).

Table 35 Cost effectiveness (eribulin versus TPC): ERG revisions to company base case

| Model scenario<br>ERG revision | Eribulin | | | TPC | | | Incremental | | | ICER | ICER |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Life years | Cost | QALYs | Life years | Cost | QALYs | Life years | Per QALY gained | Change |
| ***A. Company base case*** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | ***£35,624*** | - |
| R1) ERG use of K-M PFS data | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£37,182** | **+£1,557** |
| R2) ERG use of K-M OS data | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£35,425** | **-£199** |
| R3) Annual discounting applied | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£35,471** | **-£154** |
| R4) Correct logic error on oral vinorelbine costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£31,276** | **-£4,349** |
| R5) ERG estimated eribulin unit costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£48,199** | **+£12,575** |
| R6) ERG estimated comparator unit costs (combined with R4) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£30,106** | **-£5,518** |
| R7) ERG preferred progression utility value | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£46,912** | **+£11,288** |
| R8) ERG alternative method of costing subsequent lines of therapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£45,435** | **+£9,811** |
| R9) Correct logic error on eribulin administration costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | **£39,737** | **+£4,113** |
| ***B. ERG revised base case A+R1 to R9*** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | ***£66,043*** | ***+£30,418*** |

Costs and QALYs discounted; life years undiscounted
ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; K-M=Kaplan-Meier; ICER=incremental cost effectiveness ratio

# 7 END OF LIFE

For eribulin to be considered eligible for assessment as an end of life treatment, it is necessary that patients indicated for the treatment should have a life expectancy of less than 2 years, and that the treatment be expected to provide additional survival of at least 3 months.

The K-M analysis of the EMBRACE trial individual patient data allows both these criteria to be considered. The ERG's view is that:

- the mean OS of patients receiving TPC is 13.53 months (95% CI 11.87 to 15.19 months), indicating that survival is much lower than 2 years

- the mean OS gain attributable to treatment with eribulin is at least 3.39 months (95% CI 0.83 to 5.96 months).

# 8 KEY POINTS FOR DECISION MAKERS

## *8.1 Clinical effectiveness evidence*

**Patient population**

- The EMA (2014) indication for eribulin is for the treatment of adult patients with LABC/MBC who have progressed after one or more chemotherapy regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless these treatments were not suitable.
- The current STA focuses on patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease, i.e. only a subset of the licensed population.
- Clinical effectiveness evidence from the EMBRACE trial is presented for two populations:
    - All patients receiving ≥3 chemotherapy regimens for LABC/MBC (ITT population): patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable
    - Subgroup 2: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated). Prior treatment also includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable.

**Comparators**

- The comparators listed in the final scope issued by NICE are vinorelbine, capecitabine and gemcitabine. The company presents evidence for eribulin versus TPC for both the ITT and the Subgroup 2 populations. The ERG considers the use of TPC to be pragmatic and to reflect the likely patient experience in England.
- For the ITT population, options for TPC included vinorelbine, capecitabine and gemcitabine, as well as additional agents which included, but were not limited to, (re-challenge with) anthracyclines and taxanes
- For the Subgroup 2 population, TPC options were the same as the TPC options for the ITT population with the exception that they largely excluded treatment with capecitabine (since all patients in Subgroup 2 had been previously treated with capecitabine).The Subgroup 2 population, therefore, includes some patients who are even more heavily pre-treated than the ITT population. Indeed, approximately 65% of the Subgroup 2 population had received ≥3 prior regimens in the LABC/MBC setting compared with approximately 57% of the ITT population.

**Clinical trial evidence**

- The majority of evidence is derived from the EMBRACE trial, which is a good quality multi-centre, phase III, open-label, randomised parallel two-arm trial. The majority of patients (73%) had received prior capecitabine and the median number of cycles of eribulin was reported to be between five and six (similar to that reported in audits of eribulin use via the CDF). The findings from the EMBRACE trial show eribulin to be superior to TPC in terms of median OS and median PFS for the ITT population and for patients in Subgroup 2. AE data demonstrate an acceptable safety profile for treatment with eribulin versus TPC.

**'Real world' evidence**

- The 'real world' evidence provides additional support for the safety of eribulin (median four to six cycles) in relatively heavily pre-treated patients (≥3 previous lines of chemotherapy for LABC/MBC; ≥80% received previous treatment with capecitabine).

**Health-related quality of life**

- HRQoL data collected via the EORTC QLQ-C30 questionnaire are provided for all patients and third-line patients from Study 301. No patient received later lines of treatment and no patient had received previous treatment with capecitabine. Therefore, the generalisability of HRQoL data from Study 301 to the ITT population or Subgroup 2 patients may be questioned.

## *8.2 Cost effectiveness evidence*

**Population**

- Cost effectiveness evidence is only presented for the Subgroup 2 population for the comparison of treatment with eribulin versus TPC.

**Model related issues identified by the ERG**

- **Survival**: there is a continuing advantage for patients treated with eribulin, even after confirmation of disease progression
- **Costs**:
    - a BSA specific to patients with breast cancer with treatment that is not intended to be neo-adjuvant, adjuvant or palliative, rather than one relating to all women with breast cancer, should have been employed to estimate drug costs. Use of the BSA standard error instead of the standard deviation in the calculations provides underestimates of the cost of treatment
    - the cost of treatment with oral vinorelbine, and thus the cost of the comparator (TPC), is an underestimate
    - the estimation of the cost of further lines of chemotherapy beyond eribulin or TPC as third-line therapy is an underestimate of the true costs to the NHS
    - there is an error in the method used to cap doses
    - variation in dose intensity is not implemented in the company base case and, therefore, has no impact on the company's base case results.
- **HRQoL**: the utility value employed by the company to represent HRQOL in the progressed health state is implausible.
- **Discounting**: continuous, rather than annual, discounting of costs and benefits has been employed by the company.
- **PSA**: the company has not adequately explored the impact of parameter uncertainty.
- **Other issues**: (which have no substantial impact on cost effectiveness results) relate to the use of two different estimates of days in the year (one taking into account leap years), and structuring the model on monthly cycles for treatments that are prescribed weekly or on a 3-weekly basis.

**Cost effectiveness results**

- The company's base case ICER, for the Subgroup 2 population, for the comparison of the cost effectiveness of treatment with eribulin versus TPC is £35,625 per QALY gained
- Following the implementation of all the ERG's amendments the company's base case ICER increases by £30,418 to £66,043 per QALY gained.

**End of life**

- The treatment is indicated for patients with a life expectancy of less than 24 months and although the OS gain, experienced by patients in the EMBRACE trial who received eribulin, does not achieve statistical significance, due to the limited number of patients in the trial, the ERG is reasonable confident that eribulin offers an extension to life of at least an additional 3 months compared to current NHS treatment for Subgroup 2 patients.

# 9 OVERALL CONCLUSIONS

## *9.1 Efficacy data*

Mature efficacy data from the EMBRACE trial (a good quality multi-centre, phase III, open-label, randomised parallel two-arm trial of 762 patients) show that treatment with eribulin is superior to TPC for the ITT and Subgroup 2 populations. In particular, it appears that treatment with eribulin extends OS for patients who have been heavily pre-treated.

## *9.2 Safety data*

Data from the EMBRACE trial and observational studies also suggest eribulin has an acceptable safety profile in heavily pre-treated patients.

## *9.3 NHS clinical practice*

The median number of cycles with eribulin was reported to be between five and six in the EMBRACE trial (similar to that reported in audits of eribulin use via the CDF). The EMBRACE trial results appear to be generalisable to NHS clinical practice.

## *9.4 Cost effectiveness*

In terms of cost effectiveness, the ERG considers that the company substantially underestimates the size of the most probable base case ICER per QALY gained for eribulin versus TPC in the Subgroup 2 population. The company's base case ICER is £35,624 per QALY gained, which is £30,418 less than the ICER estimated by the ERG (£66,043 per QALY gained).

## *9.5 Implications for research*

All of the apparent survival gain for patients in the EMBRACE trial appears to occur during the post-progression survival period. Further research into whether this is common in other clinical studies and, if so, exploration as to why, may improve current understanding of LABC/MBC.

HRQoL evidence is lacking for the population of patients receiving eribulin as a >3 chemotherapy regimen for LABC/MBC. Further research into HRQoL in more heavily pre-treated patients is warranted.

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# 11 APPENDICES

## *11.1 Literature search for health-related quality of life studies*

Full details of the search terms used by the company to locate HRQoL evidence are reported in the CS (Section 5.4 and Appendix 2). The company states that they searched the following two databases: Medline (via PubMed) and Embase (via Scopus). The date of the searches (23 December 2015) and the full date span (1 January 2009 to 30 November 2015) are appropriately reported by the company (CS, Appendix 2).

The company also conducted hand searches of four conference sites on 23 December 2015: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Association for Cancer Research (AACR) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). One clinical trial registry (clinicaltrials.gov) was also searched (12 February 2016).

The ERG considers that the search terms used by the company were relevant for the databases searched. The use of free text only was appropriate as the databases that were searched did not have a Medical Subject Headings search function. However, the ERG notes that Scopus does not include all references that are included in Embase. Nonetheless, in general, the ERG is confident that the company's literature search for HRQoL evidence will have identified all relevant HRQoL studies.

The CS provides a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies. These are described in Table 36. Two reviewers independently undertook study selection in two stages:

- Stage 1 – review of abstracts
- Stage 2 – review of full text papers.

After applying the eligibility criteria to the full texts, all papers meeting the inclusion criteria were retained for data extraction. The methods used for data extraction are not specified in the CS.

Table 36 Inclusion and exclusion criteria for HRQoL evidence for patients receiving ≥3 chemotherapy regimens for LABC/MBC

| Parameter | Inclusion | Exclusion |
|---|---|---|
| Population | Adult patients AND<br>[MBC OR<br>Advanced breast cancer (ABC)] AND<br>AND 3L+ | Non-human OR<br>Children OR<br>Adolescents OR<br>Males OR<br>Studies with a unique focus on patients from outside Europe/USA were excluded |
| Intervention | Eribulin (monotherapy) | All other treatments or combinations |
| Comparator | Any | |
| Outcomes | Utilities/ disutilities/ QALYs for health states of adverse events OR<br>Quality of life assessment including EQ-5D, QLQ-C30, BR-23, FACT, SF-36, SF-6D | All others |
| Study design | Reports of mapping exercises for any outcome measure to utility OR<br>Reports of utility elicitation exercises OR<br>Reports for utility validation exercises OR<br>Reports of economic evaluations using<br>utility measures elicited during the studies OR<br>Reports of clinical trials assessing HRQOL | Editorials OR Notes OR<br>Comments OR RWE OR Letters OR<br>Other Reviews OR<br>Abstracts without full paper available<br>OR Phase I studies |
| Language | English | Non-English studies |

ABC=advanced breast cancer; MBC=metastatic breast cancer; QALY=quality adjusted life year
Source: CS, Table 53

## *11.2 Statistical analyses conducted in the EMBRACE trial*

The patient populations used for the analysis of the EMBRACE trial outcomes are summarised in Table 37.

Table 37 Patient populations used for the analysis of the EMBRACE trial outcomes

| Population | Description |
|---|---|
| Intention-to-treat (ITT) population | All patients who were randomised, irrespective of whether or not they actually received study treatment or whether they received the medication they were randomised to |
| Per protocol (PP) population | All patients in the ITT population who met the major inclusion criteria for the study, and who did not have any other major protocol violation. Major violations included patients who were treated on the opposite treatment group than the one to which they were randomised |
| Response evaluable population | All patients with measurable disease, defined as the presence of at least one measurable lesion, using RECIST criteria. This was identified by independent review |
| Safety population | All patients who were randomised and who received at least a partial dose of study treatment. The population was based on the actual treatment received |

A summary of the statistical analyses performed for the EMBRACE trial efficacy outcomes are provided in Table 38. The primary analysis was planned to occur when 411 deaths had been recorded, although the data cut-off point for the primary analysis was actually after 422 (55%) patients had died (12 May 2009). The company outlines that an updated analysis of OS was conducted at the request of the regulatory authorities, when 77% of deaths had occurred, representing a more mature dataset with longer follow up (3 March 2010 data cut-off point). The most recent OS analysis was performed after 95% of patients had died (17 June 2013), and the company presented data for Subgroup 2 patients using this most recent data cut-off, although the ERG requested that analyses on the ITT population also be performed using this data cut-off point for comparability between Subgroup 2 and the ITT population. The company obliged and results for both the ITT population and Subgroup 2 populations using the most recent data cut-off point are provided in Section 4.8 of this ERG report.

Table 38 Summary of statistical analyses for efficacy outcomes in the EMBRACE trial

| | Statistical analysis | Data management, patient withdrawals |
|---|---|---|
| **Primary outcome (OS)** | • Compared between the randomised treatment groups in the ITT population using a two-sided stratified log-rank test at a significance level of 0.049<br>• Test was stratified by HER2 status, prior capecitabine treatment, and geographical region<br>• Kaplan-Meier survival curves were used to summarise the OS, using 95% limits at selected time points<br>• Kaplan-Meier estimate of the median survival time, and first and third quartiles was presented with 95% CIs<br>• HR was presented based on fitting a Cox regression model and was stratified according to the type of treatment received, HER2 status, prior capecitabine treatment and geographical region<br>• An additional Cox regression model was fitted in which the HR was also adjusted for the number of prior chemotherapy regimens and ER status (covariates) | • Primary analysis of the primary outcome (OS) was compared between the eribulin and TPC groups in the ITT population<br>• These analyses were also performed on the PP population<br>• For patients for whom a date of death was not recorded, i.e., those who were lost to follow-up or who were alive at the date of data cut-off, time to death was censored at the time of last contact |
| **Secondary outcomes** | • Analyses were conducted based on both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data<br>• Kaplan-Meier plots and the Kaplan-Meier estimates of the medians, and first and third quartiles were presented with the 95% CI for PFS and duration of response<br>• PFS was compared between the treatment groups using a two-sided stratified log-rank test at the 5% significance level<br>• ORR was analysed using exact Pearson Clopper 2-sided 95% confidence limits for the tumour response rates in each treatment group, and was statistically compared between the two treatment groups using a Fisher's Exact Test | • PFS was assessed in both the ITT and PP populations<br>• The response evaluable population was considered the primary population for the analysis of ORR<br>• For the analysis of PFS, patients who had not progressed on the data cut-off date or who were lost to follow-up, were censored at that date |

CI=confidence interval; DoR=duration of response; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; ITT=intent-to-treat; K-M=Kaplan-Meier; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PP=per protocol; TPC=Treatment of Physician's Choice
Source: Adapted from Table 13 of the CS

### *11.3 Baseline characteristics in the EMBRACE trial*

During the clarification process, the ERG requested the company present the same baseline characteristics for Subgroup 2 patients as the ITT population, and vice versa. These are summarised below in Table 39. As highlighted in Section 4.6 of this ERG report, the baseline characteristics were distributed evenly across the treatment arms in both the ITT population and Subgroup 2 population, with the exception of cancer staging at diagnosis (data not presented in CS). Furthermore, the baseline characteristics in Subgroup 2 were broadly similar to those of the ITT population. The only exceptions were in terms of geographical region and previous lines of treatment. The latter differences are to be expected since patients had received prior capecitabine. The use of prior capecitabine also likely accounts for the differences in geographical region.

Table 39 Baseline characteristics for the EMBRACE trial - ITT population and Subgroup 2*

| Characteristic | ITT population | | | Subgroup 2 | | |
|---|---|---|---|---|---|---|
| | Eribulin (N=508) | TPC (N=254) | Total (n = 762) | Eribulin (n = 370) | TPC (n = 189) | Total (n =559) |
| Median Age (range) | 55.0 years (28 to 85) | 55.0 years (27 to 81) | 55.0 years (27 to 85) | 55.0 years (28 to 80) | 56.0 years (27 to 78) | 55.0 years (28 to 80) |
| Age distribution, n (%) | | | | | | |
| < 40 yrs | 34 (6.7) | 17 (6.7) | 51 (6.7) | 24 (6.5) | 15 (7.9) | 39 (7.0) |
| ≥ 40 – < 65 yrs | 380 (74.8) | 180 (70.9) | 560 (73.5) | 280 (75.7) | 133 (70.4) | 413 (73.9) |
| ≥ 65 yrs | 94 (18.5) | 57 (22.4) | 151 (19.8) | 66 (17.8) | 41 (21.7) | 107 (19.1) |
| Race, n (%) | | | | | | |
| Caucasian | 470 (92.5) | 233 (91.7) | 703 (92.3) | 346 (93.5) | 174 (92.1) | 520 (93.0) |
| Black | 20 (3.9) | 14 (5.5) | 34 (4.5) | 13 (3.5) | 10 (5.3) | 23 (4.1) |
| Asian/Pacific Islander | 3 (0.6) | 2 (0.8) | 5 (0.7) | 1 (0.3) | 2 (1.1) | 3 (0.5) |
| Other | 15 (3.0) | 5 (2.0) | 20 (2.6) | 10 (2.7) | 3 (1.6) | 13 (2.3) |
| Geographic region, n (%) | | | | | | |
| North America, Western Europe, Australia | 325 (64.0) | 163 (64.2) | 488 (64.0) | 258 (69.7) | 131 (69.3) | 389 (69.6) |
| Eastern Europe | 129 (25.4) | 64 (25.2) | 193 (25.3) | 77 (20.8) | 40 (21.2) | 117 (20.9) |
| Latin America, South Africa | 54 (10.6) | 27 (10.6) | 81 (10.6) | 35 (9.5) | 18 (9.5) | 53 (9.5) |
| Reproductive status, n (%) | | | | | | |
| Fertile | 46 (9.1) | 20 (7.9) | 66 (8.7) | 33 (8.9) | 14 (7.4) | 47 (8.4) |
| Post-menopausal | 379 (74.6) | 199 (78.3) | 578 (75.9) | 280 (75.7) | 150 (79.4) | 430 (76.9) |
| Surgically sterile | 78 (15.4) | 35 (13.8) | 113 (14.8) | 53 (14.3) | 25 (13.2) | 78 (14.0) |
| Infertile | 5 (1.0) | 0 | 5 (0.7) | 4 (1.1) | 0 (0.0) | 4 (0.7) |
| Median time since original diagnosis (range) | 5.4 years (0.1, 37.4) | 5.1 years (0.6, 22.9) | 5.2 years (0.1, 37.4) | 5.7 years (0.1, 37.4) | 5.3 years (0.6, 22.9) | 5.6 years (0.1, 37.4) |
| ER Status, n (%)† | | | | | | |
| + | 336 (70.0) | 171 (70.4) | 507 (70.1) | 257 (72.0) | 130 (70.7) | 387 (71.5) |
| – | 143 (29.8) | 72 (29.6) | 215 (29.7) | 99 (27.7) | 54 (29.3) | 153 (28.3) |
| Unknown | 1 (0.2) | 0 | 1 (0.1) | 1 (0.3) | 0 | 1 (0.2) |

| Characteristic | ITT population | | | Subgroup 2 | | |
|---|---|---|---|---|---|---|
| | Eribulin (N=508) | TPC (N=254) | Total (n = 762) | Eribulin (n = 370) | TPC (n = 189) | Total (n =559) |
| PR Status, n (%)† | | | | | | |
| + | 254 (56.2) | 123 (54.7) | 377 (55.7) | 195 (57.9) | 93 (54.4) | 288 (56.7) |
| – | 197 (43.6) | 102 (45.3) | 299 (44.2) | 141 (41.8) | 78 (45.6) | 219 (43.1) |
| Unknown | 1 (0.2) | 0 | 1 (0.1) | 1 (0.3) | 0 | 1 (0.2 |
| HER2 status, n (%)† | | | | | | |
| + | 83 (18.0) | 40 (17.2) | 123 (17.8) | 60 ( 17.3) | 29 ( 16.3) | 89 ( 17.0) |
| – | 373 (81.1) | 192 (82.8) | 565 (81.6) | 285 ( 82.4) | 149 ( 83.7) | 434 ( 82.8) |
| Unknown | 4 (0.9) | 0 | 4 (0.6) | 1 (0.3) | 0 | 1 (0.2) |
| Triple negative (ER/PR/HER2-negative), n (%)† | 93 (18.3) | 51 (20.9) | 144 (19.8) | 68 (18.4) | 38 (20.1) | 106 (19.0) |
| No. of organs involved‡, n (%) | | | | | | |
| 1 | 85 (16.7) | 35 (13.8) | 120 (15.7) | 61 (16.5) | 25 (13.2) | 86 (15.3) |
| 2 | 172 (33.9) | 82 (32.3) | 254 (33.3) | 128 (34.6) | 59 (31.2) | 187 (33.4) |
| 3 | 145 (28.5) | 77 (30.3) | 222 (29.1) | 106 (28.6) | 60 (31.7) | 166 (29.7) |
| 4 | 71 (14.0) | 37 (14.6) | 108 (14.2) | 49 (13.2) | 29 (15.3) | 78 (14.0) |
| 5 | 24 (4.7) | 16 (6.3) | 40 (5.2) | 18 ( 4.9) | 10 ( 5.3) | 28 ( 5.0) |
| ≥ 6 | 9 (1.8) | 7 (2.8) | 16 (2.1) | 6 ( 1.6) | 6 ( 3.2) | 12 ( 2.1) |
| Tumour sites in > 10% patients overall, n (%) | | | | | | |
| Bone | 306 (60.2) | 158 (62.2) | 464 (60.9) | 234 (63.2) | 120 (63.5) | 354 (63.3) |
| Liver | 296 (58.3) | 159 (62.6) | 455 (59.7) | 225 (60.8) | 127 (67.2) | 352 (63.0) |
| Lymph nodes | 220 (43.3) | 118 (46.5) | 338 (44.4) | 150 (40.5) | 87 (46.0) | 237 (42.4) |
| Lung | 197 (38.8) | 95 (37.4) | 292 (38.3) | 138 (37.3) | 67 (35.4) 34 (18.0) | 205 (36.7) |
| Pleura | 87 (17.1) | 42 (16.5) | 129 (16.9) | 62 (16.8) | 13 (6.9) | 96 (17.2) |
| Breast | 54 (10.6) | 24 (9.4) | 78 (10.2) | 30 (8.1) | | 43 (7.7) |
| ECOG performance status, n (%) | | | | | | |
| 0 | 217 (42.7) | 103 (40.6) | 320 (42.0) | 154 (41.6) | 80 (42.3) | 234 (41.9) |
| 1 | 244 (48.0) | 126 (49.6) | 370 (48.6) | 179 (48.4) | 90 (47.6) | 269 (48.1) |
| 2 | 39 (7.7) | 22 (8.7) | 61 (8.0) | 30 (8.1) | 16 (8.5) | 46 (8.2) |

| Characteristic | ITT population | | | Subgroup 2 | | |
|---|---|---|---|---|---|---|
| | Eribulin (N=508) | TPC (N=254) | Total (n = 762) | Eribulin (n = 370) | TPC (n = 189) | Total (n =559) |
| No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%) | | | | | | |
| 1 | 1 (0.2) | 0 | 1 (0.1) | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| 2 | 65 (12.8) | 31 (12.2) | 96 (12.6) | 17 (4.6) | 11 (5.8) | 28 (5.0) |
| 3 | 176 (34.6) | 83 (32.7) | 259 (34.0) | 122 (33.0) | 51 (27.0) | 173 (30.9) |
| 4 | 166 (32.7) | 79 (31.1) | 245 (32.2) | 142 (38.4) | 69 (36.5) | 211 (37.7) |
| 5 | 85 (16.7) | 51 (20.1) | 136 (17.8) | 74 (20.0) | 48 (25.4) | 122 (21.8) |
| ≥ 6 | 13 (2.6) | 9 (3.5) | 22 (2.9) | 13 (3.5) | 9 (4.8) | 22 (3.9) |
| No. of prior regimens in LABC/MBC setting, n (%) | | | | | | |
| 0 | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| 1 | 8 ( 1.6) | 7 (2.8) | 15 (2.0) | 2 (0.5) | 2 (1.1) | 4 (0.7) |
| 2 | 219 (43.1) | 90 (35.4) | 309 (40.6) | 130 (35.1) | 53 (28.0) | 183 (32.7) |
| 3 | 163 (32.1) | 83 (32.7) | 246 (32.3) | 132 (35.7) | 67 (35.4) | 199 (35.6) |
| 4 | 92 (18.1) | 55 (21.7) | 147 (19.3) | 81 (21.9) | 48 (25.4) | 129 (23.1) |
| 5 | 21 (4.1) | 13 (5.1) | 34 (4.5) | 21 (5.7) | 13 (6.9) | 24 (6.1) |
| ≥ 6 | 4 (0.8) | 5 (2.0) | 9 (1.2) | 4 (1.1) | 5 (2.6) | 9 (1.6) |
| Duration of last chemotherapy (months), Median (min, max)† | 3.57 (0.0, 32.0) | 3.50 (0.1, 25.3) | 3.53 (0.0, 32.0) | 3.8 (0.0, 32.0) | 3.7 (0.1, 25.3) | 3.7 (0.0, 32.0) |
| No. of patients who previously (adjuvant and LABC/MBC setting) received: n (%) | | | | | | |
| Taxanes | 503 (99.0) | 251 (98.8) | 754 (99.0) | 365 (98.6) | 186 (98.4) | 551 (98.6) |
| Anthracyclines | 502 (98.8) | 250 (98.4) | 752 (98.7) | 365 (98.6) | 185 (97.9) | 550 (98.4) |
| Capecitabine | 370 (72.8) | 189 (74.4) | 559 (73.4) | 370 (100.0) | 189 (100.0) | 559 (100.0) |

ECOG=eastern cooperative oncology group; ER=oestrogen receptor; HER2=human epidermal growth factor receptor 2; ITT=intent-to-treat; LABC=locally advanced breast cancer; PR=progesterone receptor; TPC=treatment of Physician's Choice

*Table excludes missing data for all characteristics

†For the ER, PR, HER2 and triple negative status, the percentages are calculated from the total number of patients tested

‡The number of organs involved was based on the investigator review data

Source: Company response to the ERG clarification letter, Table A2 and company response to further ERG clarification

## *11.4 Additional ERG observations on the quality assessment of the randomised controlled trials*

In both trials, patients and investigators were not blinded to treatment allocation. From a pragmatic point of view, this is reasonable given that the administration and scheduling of agents in the intervention and comparator arms differed in both trials, particularly in the EMBRACE trial where TPC entailed a number of possible treatment options. However, it can be considered a weakness, increasing the risk of bias. However, the ERG notes that for the EMBRACE trial, an independent data monitoring committee (DMC) reviewed the safety of eribulin treatment and assessed the interim efficacy data and the trial sponsor remained blinded to OS data until database lock. In addition to investigator review of outcomes relating to tumour response (PFS and ORR), independent assessment of PFS and ORR were also undertaken. Results of the independent assessments, compared with investigator assessments are summarised in the main body of the report, Section 4.8.2.

For the results of a trial with so many centres to be meaningfully interpreted, the manner in which the protocol is implemented should be clear and similar across all centres. With so many investigators in different countries, general clinical practice will always be an issue and the results of a trial can only be generalisable if it is executed efficiently. The CSR of the EMBRACE trial states that study monitors were responsible for establishing and maintaining regular contact between study centres and the company. Monitors made regular visits to each study centre (maximum time between visits was 6 weeks) to check adherence to the protocol and inform the company of any issues arising. The monitor provided written reports to the company after each contact with the study centre. The ERG is confident that the company made every effort to ensure that the trial procedures were implemented comprehensively across all study centres.

## *11.5 Health-related quality of life data reported for all patients*

The HRQoL findings reported in the CS for all patients in Study 301 are summarised in Table 40. It is important to note that only 28% of these patients received eribulin as a third-line treatment for LABC/MBC and no patient had been previously treated with capecitabine.

Table 40 Health-related quality of life data reported in Study 301 - all patients

| Domain | Results summarised in CS* |
|---|---|
| Global GHS/QoL (QLQ-C30) | Overall, the median global health status (GHS)/ quality of life (QoL) scores were similar between the eribulin and capecitabine groups: Mean scores around 50 suggest significant impact of disease<br>Median time to symptom worsening (TSW) was similar for both arms<br>The majority of patients (≥74%) in both treatment groups maintained or improved their GHS/ QoL versus baseline using minimum important differences (MID) analysis † |
| Functional | |
| QLQ-C30: cognitive; emotional; physical; social; role | There were no differences between the two treatment arms in terms of impact on patients' functioning over time, as measured by changes in EORTC QLQ-C30 scores for functional scales<br>Scores on QLQ-C30 functional scales were generally good (mean values around and above 70)<br>10% to 35% of patients in both treatment arms experienced a clinically significant worsening of their functioning |
| QLQ-BR23: body image; future perspective; sexual enjoyment; and sexual functioning | Breast-cancer-specific functional scales of the QLQ-BR23 questionnaire showed impact on all domains for eribulin (mean scores 32 to 65), in particular, on sexual functioning (mean score 14)<br>Patients receiving eribulin had comparatively worse scores on the body image ($p<0.001$) and sexual functioning scales ($p<0.05$), measured by QLQ-BR23, than those receiving capecitabine<br>10% to 35% of patients in both treatment arms experienced a clinically significant worsening of their functioning<br>No statistically significant differences over the course of the study were observed between the treatment groups, except that a higher proportion of patients receiving capecitabine reported a meaningful worsening on the future perspective scale than those receiving eribulin (MID 10; HR=1.173 [95% CI=1.015, 1.356]; $p<0.05$) † |
| Symptoms | |
| QLQ-C30: appetite loss; constipation; diarrhoea; dyspnoea; fatigue; financial difficulties; insomnia; nausea and vomiting; pain | Patients receiving capecitabine had comparatively more severe symptoms (that is, higher symptom scores) for nausea and vomiting ($p<0.001$) and diarrhoea ($p<0.001$) and shorter TSW for all these symptoms ($p<0.05$) compared with those treated with eribulin ¥ |
| QLQ-BR23: arm symptoms; breast symptoms; systemic therapy side-effects; and upset by hair loss | Patients receiving eribulin had worse mean scores for other systemic therapy side-effects including dry mouth, different tastes, irritated eyes, feeling ill, hot flushes, headaches, and hair loss (all $p<0.001$), and upset by hair loss ($p<0.05$) and shorter TSW for all these symptoms ($p<0.05$) compared with those treated with capecitabine ¥ |

*Note: All scores for the EORTC QLQ-C30 and EORTC QLQ-BR23 were transformed to a scale from 0 to 100 as described in the EORTC manual[59]

† MID was defined as smallest difference in scores between groups in the scales of interest, which patients perceived as beneficial; literature-based threshold values for MID were used for scales in the EORTC QLQ-C30[60] and because there are no published MIDs on the QLQ-BR23, a 10-point change was considered consistent with previous estimates[61]

Source: CS, pp94 to 100

¥ TSW was defined as time until clinically meaningful deterioration by a specified threshold for each patient-reported endpoint; TSW was calculated for each HRQoL scale using Kaplan-Meier curves

### *11.6 ERG Revisions to company's model*

All revisions are activated by a logic switch with 0 = unchanged, 1 (or any non-zero number) = apply ERG modification.

Logic switches are indicated by range variables Mod_*n* where n = 1 – 9 (n=2 not used).

A menu of revisions/Mod numbers appears on the 'Results' worksheet together with summary results as used to transfer to the ERG report

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| ERG Table X2 Row Title | Associated detail | Implementation instructions |
|---|---|---|
| R1. ERG PFS estimates<br><br>(Binary switch Mod_1) | ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival' | In Sheet 'Appendix Partition'<br><br>**Replace** formula in cell E8 by<br>=IF(Mod_1=1,ERG_survival!D4,<br>INDEX(EXT_data,MATCH($B8,EXT_Cycle,0),<br>MATCH(E$5&E$7&$P$9&$P$8&$W$9,EXT_Key,0)))<br>**Copy** formula in cell E8 to range E9:E248<br><br>**Replace** formula in cell F8 by<br>=IF(Mod_1=1,ERG_survival!F4,<br>INDEX(EXT_data,MATCH($B8,EXT_Cycle,0),<br>MATCH(F$5&F$7&$P$9&$P$8&$W$9,EXT_Key,0)))<br>**Copy** formula in cell F8 to range F9:F248 |
| R2. ERG OS estimates<br><br>(Binary switch Mod_2) | ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival' | In Sheet 'Appendix Partition',<br><br>**Replace** formula in cell G8 by<br>=IF(Mod_2=1,ERG_survival!E4,<br>INDEX(EXT_data,MATCH($B8,EXT_Cycle,0),<br>MATCH(G$5&G$7&$P$9&$P$8&$W$7,EXT_Key,0)))<br>**Copy** formula in cell G8 to range G9:G248<br><br>**Replace** formula in cell H8 by<br>=IF(Mod_2=1,ERG_survival!G4,INDEX(EXT_data,<br>MATCH($B8,EXT_Cycle,0),<br>MATCH(H$5&H$7&$P$9&$P$8&$W$7,EXT_Key,0)))<br>**Copy** formula in cell H8 to range H9:H248 |
| R3. Discounting method<br><br>(Binary switch Mod_3) | None | In Sheet 'Appendix PSA',<br><br>**Replace** formula in cell C63 by<br>=1/((1+$I$19)^IF(Mod_3=0,B63,INT(B63/12)))<br>**Replace** formula in cell D63 by<br>=1/((1+$I$18)^IF(Mod_3=0,B63,INT(B63/12)))<br>**Copy** range C63:D63<br>**Paste** to range C64:D123 |

| ERG Table X2 Row Title | Associated detail | Implementation instructions |
|---|---|---|
| | | In Sheet 'Appendix Transition',<br><br>**Replace** formula in cell K19 by =IF(Mod_3=1,1/((1+Discounting_cost)^(12*INT(D19))), 1/((1+Discounting_cost)^(B19)))<br>**Replace** formula in cell L19 by =IF(Mod_3=1,1/((1+Discounting_ben)^(12*INT(D19))), 1/((1+Discounting_ben)^(B19)))<br>**Replace** formula in cell M19 by =IF(Mod_3=1,1/((1+Discounting_ben)^(12*INT(D19))), 1/((1+Discounting_ben)^(B19)))<br>**Copy** range K19:M19<br>**Paste** to range K20:M259 |
| R4. Correct logic error in oral vinorelbine costing<br><br>(Binary switch Mod_7) | None | In Sheet 'Appendix dose and BSA',<br><br>**Replace** formula in cell S76 by =IF(Mod_7=1,S75*$J$53, S75*$F$53)<br>**Replace** formula in cell S77 by =IF(Mod_7=1, S76*$J$54, S76*$F$54)<br>**Replace** formula in cell S78 by =IF(Mod_7=1,P78*$H$60+R78*$J$60+$I$60*Q78, P78*$K$60+R78*$M$60+$L$60*Q78)<br>**Copy** cell S78<br>**Paste** to range S79:S138 |
| R5. ERG estimated eribulin unit costs<br><br>(Binary switch Mod_5) | ERG_Reworked_Drug_Costs(final).xlsx | In Sheet 'Appendix dose and BSA',<br><br>**Replace** formula in cell H75 by =SUMPRODUCT(($D$78:$D$138)*(H$78:H$138))*IF(Mod_5=1,1.441618,1)<br><br>**Replace** formula in cell I75 by =SUMPRODUCT(($D$78:$D$138)*(I$78:I$138))*IF(Mod_5=1,1.441618,1) |

| ERG Table X2 Row Title | Associated detail | Implementation instructions |
|---|---|---|
| R6. ERG estimated comparator costs<br><br>(Binary switch Mod_6) | ERG_Reworked_Drug_Costs(final).xlsx | In Sheet 'Appendix dose and BSA',<br>**Replace** formula in cell M75 by<br>=SUMPRODUCT(($D$78:$D$138)*(M$78:M$138))<br>*IF(Mod_6=1,1.032214,1)<br>**Replace** formula in cell N75 by<br>=SUMPRODUCT(($D$78:$D$138)*(N$78:N$138))<br>*IF(Mod_6=1,1.032214,1)<br>**Replace** formula in cell S75 by<br>=SUMPRODUCT(($D$78:$D$138)*(S$78:S$138))<br>*IF(Mod_6=1,1.272909,1)<br>**Replace** formula in cell T75 by<br>=SUMPRODUCT(($D$78:$D$138)*(T$78:T$138))<br>*IF(Mod_6=1,1.272909,1)<br>**Replace** formula in cell Y75 by<br>=SUMPRODUCT(($D$78:$D$138)*(Y$78:Y$138))<br>*IF(Mod_6=1,1.53137,1)<br>**Replace** formula in cell Z75 by<br>=SUMPRODUCT(($D$78:$D$138)*(Z$78:Z$138))<br>*IF(Mod_6=1,1.53137,1)<br>**Replace** formula in cell AF75 by<br>=SUMPRODUCT(($D$78:$D$138)*(AF$78:AF$138))<br>*IF(Mod_6=1,0.898964,1)<br>**Replace** formula in cell AG75 by<br>=SUMPRODUCT(($D$78:$D$138)*(AG$78:AG$138))<br>*IF(Mod_6=1,0.898964,1)<br>**Replace** formula in cell AM75 by<br>=SUMPRODUCT(($D$78:$D$138)*(AM$78:AM$138))<br>*IF(Mod_6=1,0.80107,1)<br>**Replace** formula in cell AN75 by<br>=SUMPRODUCT(($D$78:$D$138)*(AN$78:AN$138))<br>*IF(Mod_6=1,0.80107,1)<br>**Replace** formula in cell AT75 by<br>=SUMPRODUCT(($D$78:$D$138)*(AT$78:AT$138))<br>*IF(Mod_6=1,1.231349,1)<br>**Replace** formula in cell AU75 by<br>=SUMPRODUCT(($D$78:$D$138)*(AU$78:AU$138))<br>*IF(Mod_6=1,1.231349,1)<br>**Replace** formula in cell AZ75 by<br>=SUMPRODUCT(($D$78:$D$138)*(AZ$78:AZ$138))<br>*IF(Mod_6=1,1.19404,1)<br>**Replace** formula in cell BA75 by<br>=SUMPRODUCT(($D$78:$D$138)*(BA$78:BA$138))<br>*IF(Mod_6=1,1.19404,1) |

| ERG Table X2 Row Title | Associated detail | Implementation instructions |
|---|---|---|
| R7. ERG preferred progression utility value<br><br>(Binary switch Mod_8) | None | In Sheet 'Utility',<br><br>**Replace** formula in cell F29 by =IF(Mod_8=1,0.96,F11)<br><br>**Replace** formula in cell H29 by =IF(Mod_8=1,0.496,H11) |
| R8. ERG alternative option for costing subsequent treatments | 'Model parameters':Q13 must be set to "Maximum number of cycles" | In Sheet 'Model parameters',<br><br>**Replace** formula in cell R17 by =IF(Mod_9=1,600,6)<br><br>**Enter** in cell N92 the text *Proportion of Tx post progression*<br><br>**Replace** formula in cell P91 by =SUMPRODUCT((J79:J89)*(P79:P89))*P93<br><br>**Replace** formula in P92 by =IF(Mod_9=1, 60%,100%) |
| Additional logic adjustment to prevent 'divide by zero' errors | None | In Sheet 'Appendix – Transition',<br><br>**Replace** formula in cell V90 by =IF(F90+G90<0.0001,100%,(H96-H90)/SUM(F90:G90))<br><br>**Copy** cell V90<br><br>**Paste** formula only to range V91:V259 |